LIFE INSURANCE GRANT

1954-55

Brian J. Sproule

ABSTRACT

The term "high output" failure is used to describe a type of failure of the heart in which the cardiac output is elevated above normal levels. The exact mechanism of this variety of cardiac failure has been incompletely understood.

To elucidate the hemodynamic changes which occur, pressures were measured in the right ventricles, left ventricles, and carotid arteries of a number of dogs. Cardiac outputs, blood volumes and peripheral resistances were also determined. To facilitate these measurements, carotid arteries were brought up into skin tubes and left ventricles were affixed to the anterior chest wall. An increased cardiac output was obtained by constructing an arterio-venous fistula between the abdominal aorta and the inferior vena cava.

Twenty-six animals were operated upon and cardiac failure was produced and evaluated hemodynamically in three.

The changes that were seen were: an initially increased cardiac output with a fall from this level accompanying failure; an increased blood volume; a decreased peripheral resistance; an increase of end-diastolic pressure in the left ventricle followed later by an increase of pressure in the right ventricle.

We concluded that in the "high output" type of heart failure the first chamber to decompensate is the left ventricle.

THE UNIVERSITY OF ALBERTA

HEMODYNAMIC CHANGES IN HIGH OUTPUT CARDIAC FAILURE

A DISSERTATION

SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF ...SCIENCE.....

FACULTY OF MEDICINE

by

Brian J. Sproule

EDMONTON, Alberta,

ACKNOWLEDGEMENTS

This investigation was carried out with the assistance of grants from the Canadian Life Insurance Companies, under the direction of Dr. R. S. Fraser, to whom the writer acknowledges his indebtedness.

Thanks are due to Dr. C. A. Ross, who assisted with many of the operative procedures; to Mr. C. A. Heath, who was largely instrumental in the development of techniques for our first dye curves; and to Miss Lucy Olekshy without whose invaluable technical assistance much of the calculation and instrumentation could not have been done.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

THE PROBLEM

The problem was to determine the mechanism of heart failure in those diseases such as hyperthyroidism and beriberi which are characterized by a high cardiac output.

It is recognized that failure may be subdivided into that primarily affecting the right, and that primarily affecting the left side of the heart. It was felt that measurement of the end-diastolic pressures in both ventricular cavities might offer a way of determining, in these diseases, which side of the heart was involved first.

PART I

BACKGROUND

CARDIAC FAILURE

"It is the task of the heart to supply an adequate quantity of blood to meet the requirements of the various organs in the body at rest and during activity."[23] When it does this it is competent, providing no compensatory mechanisms are necessary for it to complete its task. If this task is not completely performed, or if compensation is necessary at ordinary levels of output, the heart is failing.

Compensatory mechanisms increase the output of a normal heart during stress, but these are not indicative of failure unless they become disproportionate (that is, unless the achieved increase in cardiac output is not as great as should be expected from the observed increase in compensatory mechanisms). The difference between the level of compensation at which the heart is operating and the level which it can attain before these mechanisms become detrimental rather than beneficial is the total cardiac reserve.

These compensatory mechanisms are four in number:

1. Dilatation.
2. Hypertrophy.
3. Tachycardia.
4. An increase in the contractile power of the myocardium.

1. Dilatation

Dilatation of the heart, while not the first mechanism called into play, is seen in the isolated heart, and is fundamental in adjusting the input to the output load. In 1914, the isolated heart was studied by Patterson and Starling and the basic relationship, now known as the "law of the heart" was formulated. They found in the heart-lung preparation

that an increase in venous return was attended by an increased cardiac output. This was accompanied at higher levels by an increased venous pressure and, eventually, by a decrease in output. The law was stated as follows: "The law of the heart is therefore the same as that of skeletal muscle; namely, that the mechanical energy set free on passage from the resting to the contracted state depends on the area of 'chemically active surfaces' i.e., on the length of the muscle fibres."(34) Sometime prior to this, in 1895, Otto Frank had postulated that changes in initial length are produced by alterations in ventricular pressure at the onset of contraction; namely, by the initial tension.(38)

Opinions vary as to whether measurement of the initial tension (the end-diastolic ventricular pressure) is a valid way of assessing the dilatation that has occurred.

Carl Wiggers states, "personal experience has confirmed Frank's earlier postulate that changes in initial length are produced by changes in initial tension. Such changes, although small, are usually discernable in optical records of sufficient amplitude.(53)

Louis N. Katz states, "in this modern era of catheterization too many physicians imagine that the pressures in the heart at the end of diastole are a good measure of the size of the heart at that time. Actually the relationship between the end diastolic volume and the end diastolic pressure is not linear but curvilinear. There is, therefore, under ordinary circumstances, little or no change in the end diastolic pressure with rather large changes in end diastolic volume. It is to the end diastolic volume change that the ventricles energy release, ability to work and pump blood is related and not to its end diastolic pressure. The difficulties of obtaining information regarding end diastolic volume should not permit

the employment of end diastolic pressure, or worse still, the average or mean atrial pressure as an index of the adjustment of the heart by dilatation to an increased load."[23]

Stanley J. Sarnoff states, "It seems that much of this debate is artificial. For in any hollow viscus an increase in its volume is accompanied by an increase in pressure and these interdependent variables bear a constant relationship to each other unless a change in elasticity or tone occurs. We consider myocardial failure to be an alteration of the contractility of the myocardial fibres resulting in a shift of the ventricle from a normal function curve to a depressed one. The increased filling pressures are thus not a cause of failure but a consequence of decreased myocardial contractility."[41]

At any rate, it is agreed that an increase in the end-diastolic ventricular pressure does indicate a change in the dynamics of ventricular contraction. Also, any errors inherent in taking it as a measure of ventricular dilatation are in the direction of discovering adjustments too late rather than too early.

The immediate factors that determine end-diastolic pressure are: the systolic residue (the blood not pumped out in the previous systole); the tone of the ventricles affecting their resistance to filling; and the duration of diastole, particularly the rapid inflow phase.[23]

There is one other factor which not only affects the pressures themselves, but more particularly affects the measurement of them. This factor is intrathoracic pressure.

Although intrathoracic pressure changes could not be studied in the isolated heart-lung preparation, Starling and his group felt that they were probably of importance.[33] More recent studies[24] have shown that

during moderately deepened respiration a distinct pattern of pressure fluctuation is seen. The difference between the pressure in the right auricle at the end of diastole and the pressure in the intrapleural space (the net auricular pressure) is increased in inhalation and lessens during exhalation. Similarly, the pressure in the right ventricle at the end of diastole in relation to the negative intrapleural pressure (the net ventricular pressure) is increased during inspiration. When measured, however, by the usual devices, the pressure is registered as being decreased during inspiration, since this factor of negative intrapleural pressure is not commonly accounted for. If the stroke volume of the ventricles varies as a function of the initial net ventricular tension an increase in output during inspiration occurs. It has been suggested that this is due to changes in the resistance of the pulmonary capillary bed.(33) Regardless of how accurately cardiac dilatation can be assessed, it has been well established that it cannot continue to take place indefinitely and produce an increase in effective cardiac work. Actually after a certain point, further dilatation leads to a decrease in work accomplished. The heart can therefore be dilated and compensated, but when over dilated it is in a state of failure.

2. Hypertrophy

Hypertrophy is another mechanism which permits the heart to release more energy to overcome an increased load. It does not become evident at once but if the load is sustained for a long time it is the most constant and most efficient adjustment. The mechanism of hypertrophy is not known -- it is associated with dilatation, with relative hypoxia and with a relative increase in the work of the heart.(23) It appears to be a complex metabolic process under the leading influence of the pituitary growth hormone; apparently enhanced by sensitizing actions of the thyroid hormone and the

adrenal mineralo-corticoids.(36,2)

Its degree can be approximately assessed by clinical examination, by x-ray studies, and by the electrocardiogram. Weight alone can not be used as a strict criterion since by using this as a reference varying amounts of fibrous tissue etc. are measured.(23)

The beneficial effects of hypertrophy are limited by the fact that the capillaries do not increase in proportion to the muscle mass. The increased mass of muscle is eventually, therefore, served by a relatively smaller number of blood vessels, and ischemia with its attendent detrimental changes in intracellular energy release supervenes.

3. Tachycardia

The third compensatory mechanism listed is tachycardia, also occurring in some manner under the influence of an increased load. The increased heart rate is apparently mediated by a lessening in tone of the cholinergic nervous mechanism and an enhancement in tone of the adrenergic nervous mechanism, aided by the release of adrenalin and nor-adrenalin together with other hormonal agents.(23) Efferent impulses from end organs in the pulmonary and systemic vascular trees, in the heart muscle itself, and in various somatic structures including the special senses are relayed through centres in the central nervous system to influence the heart rate.

The benefits of an increase in rate are limited by a number of considerations.

Firstly, from the shape of the filling curve of the ventricles it can be seen that as the heart accelerates it originally effects only an abbreviation of diastasis. Consequently the minute output will go up. This is so since stroke output depends on diastolic filling. When, however, the rate becomes so rapid that it interferes with the rapid inflow phase, then the product of the stroke volume and the heart rate will decrease.(53)

Secondly, tachycardia becomes detrimental because it cuts down the recovery time. The heart has very little ability to go into oxygen debt. It must make up in the next diastole or two for the oxygen for which it goes into debt during systole; and since it is constantly beating this cannot be out of balance for long without initiating a progressive deterioration of muscular action. As the heart accelerates, the acceleration is primarily at the expense of diastole, since systole varies only with the square root of the cycle length.(23)

Finally, it is clearly established that the mechanical efficiency, estimated in terms of O_2 consumed for work done, declines progressively as the heart accelerates; and also that, as the heart progressively speeds up, insufficiency of its coronary blood flow eventually ensues.(54)

4. Increase in Contractile Power.

The fourth and last compensatory mechanism is an increase in the contractile power of the myocardium. It, like tachycardia, is thought to be mediated by reflexogenic and hormonal mechanisms which are largely extracardiac in origin although the exact agents are not known. However, in some manner changes occur in the viscous-elastic properties of the heart (its tone) and in the machinery of the heart's systole (its contractile power). Which part or parts of the intricate machinery of fat and carbohydrate metabolism — whether glycolysis, the Krebs cycle, the actin-myosin mechanism, or the ionic mileau surrounding the muscle — are affected has not been established.

Here, once again, it would appear that these changes occur with benefit to a certain point beyond which the changes rapidly become detrimental. "It can be stated that myocardial weakness leading to congestive heart failure seems to be caused largely and jointly by the detrimental

interference of exaggerated adreno-sympathogenic catecholamine action on myocardial oxidative energy economy, and by the distorting influence of adrenal mineralo-corticoids on myocardial electrolyte balance (increase of intracellular sodium, decrease of potassium). Linked up with these changes are probably alterations in carbohydrate and phosphate metabolism, membrane potentials and depolarization, and actin-myosin contractility."(36)

These then, are the compensatory mechanisms by means of which the heart, under stress, increases its output, and which, when not present in a degree commensurate with the increased level of work attained are the first signs of failure of the heart. Tachycardia can be measured directly. Dilatation, hypertrophy and increase in contractile power of the heart can be indirectly estimated by various means. These measurements and estimations are our first indications of failure.

Later on in the process more overt indications of cardiac failure supervene. The obvious one is congestion in regions of the circulation behind the failing part of the heart. A strictly mechanical explanation for this phenomenon is easy to visualize — a "damming up" of fluid behind the region of failure. If it takes place on the left side (behind the left ventricle) — we have pulmonary congestion, impaired pulmonary ventilation, pulmonary edema first manifested by rales, and finally pulmonary arterial hypertension. From here it can carry on through the circuit of the right side of the heart. Such congestion in the systemic veins (behind the right ventricle) leads to venous engorgement, liver enlargement, ascites, peripheral edema and interference with the function of all the organs. These states are popularly called left sided failure and right sided failure.

This does not mean that the failing side of the heart is putting out less blood than the other side. "A moment's reflection will show that

if the left heart were to pump 5 c.c. more per stroke than the right and if the right ventricle pumped 60 c.c. per stroke and the heart beat 80 times per minute and if the circulating blood volume is of the order of 5 litres then in about 10 minutes all of the blood would have been pumped into the systemic circuit and none would remain in the lungs."(23)

Eugene Stead is of the opinion that for brief periods the right ventricle may pump blood into the lungs at a faster rate than the left ventricle pumps it out.(11) This, he feels, can occur by a combination of two mechanisms: (1) by allowing the right atrial pressure to fall and (2) by active constriction of the systemic venous bed.(12)

No investigator, however, has been able to advance a similar explanation for right ventricular failure -- it is obvious that the vasculature of the lungs cannot by active constriction deliver enough blood to the left side of the heart to flood the peripheral circulation. There must, therefore, be some other mechanism for an increase in venous pressure.

Many theories have been advanced for this phenomenon. One explanation is that blood is brought out of the reservoirs and the venules by a neurogenic and humoral mechanism in an attempt to bring about compensatory dilatation of the incompetent chamber of the heart.(23)

McMichael and his group feel that a venopressor mechanism is very important.(31)

The basic stimulus is probably anoxia at the tissue level, either from an absolute decrease of cardiac output or a relative decrease due to increased tissue metabolism. In the early stages of failure this stimulus may only occur with activity and increased filling pressure, which maintains compensation when needed is beneficial; but with increasing levels it is harmful, decreasing the cardiac output below the optimum level.

Another explanation for the rising venous pressure is that it is due to an increase in blood volume.[13] It has been well substantiated that this does indeed occur in heart failure, at least in its later stages.[29,39]

Most workers consider this hypervolemia to be due to a retention of sodium and therefore of water as a result of failure of the renal elimination of sodium. There are several theories as to the means by which this is affected.

Merrill and others feel that a relatively or absolutely reduced cardiac output is primary in causing a reduction of sodium excretion.[30,57] The reduction of renal plasma flow and filtration rate thus effected is enhanced by a contraction of the efferent arterioles of the kidney which is probably mediated by some hormone.

Extensive investigation into the role of hormonal factors leaves little doubt that the adrenal gland and the posterior lobe of the pituitary play an important part in causing retention of sodium and water.[19]

Katz offers experimental proof that neither a reduction of renal plasma flow and the glomerular filtration rate or an increase in venous pressure in the renal veins will cause retention of sodium chloride and water.[4] His work would indicate that "it is not stasis in any special area like the head, the kidney, the liver or the endocrines per se, which causes sodium chloride and water dysfunction of the kidney, but it is stasis, per se, since stasis even in a region not involving such organs can lead to a similar disturbance. Whether it is local venous hypervolemia or elevated venous pressure, or transudation, or local changes in the tissues, or a tendency towards hypervolemia in the rest of the circulation when part of the blood is impounded which is the trigger mechanism cannot be said.[23]

Generalized peripheral edema, hepatic congestion, ascites and congestion of the gastro-intestinal tract are related in a fairly obvious way to the high venous pressure and the increase in blood volume.

Also related to congestion and stasis, in a less obvious way, is a degree of peripheral arterial oxygen unsaturation which may or may not be manifested by cyanosis. Since the circulation is generally slowed in cardiac failure there is increased de-oxygenation of capillary blood. This in turn leads to an increased difference between arterial and venous oxygen content. If the total amount of reduced hemoglobin exceeds 5 grams per 100 c.c. of blood, cyanosis is usually evident. It can be readily seen that in polycythemia a much smaller percentage of reduced hemoglobin would give rise to clinical cyanosis than it would in anemia.(12)

We have now outlined the ways in which the heart reacts to stress, the compensatory mechanisms that it employs to overcome the stress, and the reasons for and the end results of inadequacy of these compensatory mechanisms.

Stress upon the heart may perhaps be subdivided three ways. It may be due to: (a) An increase in its input load -- i.e. in venous return. (b) An increase in its resistance load -- i.e. in the blood pressure in the systemic or pulmonary arterial systems. (c) Certain hidden loads not so easily defined.

The venous return may be increased in any process associated with increased body metabolism, in anemia, in hypoxemia and in certain vitamin deficiencies. The innumerable theories on the causes of increase in the blood pressure in the systemic and pulmonary vessels are beyond the scope of this discussion. The hidden loads may be conditions such as valvular obstructions and regurgitations, intrinsic disease of the myocardium, and shunts.(1)

HIGH OUTPUT FAILURE

The conditions in which we are particularly interested are those in which there is a high level of cardiac output. The heart in these conditions fails in precisely the same way, as outlined above, that the hearts with a normal or low cardiac output fail.

The same compensatory mechanisms are seen early in failure and the same sequelae of congestion with its attendent symptomatology indicate that the compensatory mechanisms are becoming inadequate. Here, too, as the heart becomes an inefficient pump, the cardiac output drops. True enough, this output may still be larger than normal, but it is smaller than it was, and it is decreased relative to the needs of the circulatory system it is supplying.

The conditions in which the cardiac output is elevated above the normal range are severe anemia, hyperthyroidism, certain types of chronic pulmonary disease, patent ductus arteriosus, Paget's disease, beri-beri and arterio-venous fistula. As measured by the Fick principle the cardiac output is determined by two factors:

1. The arterial-mixed venous oxygen difference and,
2. The oxygen consumption per minute.

A rise in metabolism without any increase in A-V oxygen difference or a decrease in A-V difference without a fall in metabolism both indicate a rise in cardiac output.(45) In each of the above conditions one or another of these changes hold.

Also, in each instance, there is reduced resistance to the run-off of blood from the systemic arterial tree. Most of the total peripheral resistance resides in the arterioles of the systemic circuit, where relatively viscous blood flows through very small tubes. The main bases for a decrease in the peripheral resistance are:

1. Shunts, which channel the blood around the resistance interposed by the arterioles.
2. Dilatation of the arterioles.
3. Lowered viscosity of the blood.

If we now look at the list of diseases leading to the high output failure syndrome, we can attribute the decreased peripheral resistance to shunts in arterio-venous fistula, patent ductus arteriosis and Paget's disease; to arteriolar dilatation in beri-beri, hyperthyroidism and possibly in anemia; and to lowered viscosity of the blood in severe anemia. In some cases of chronic pulmonary disease a slight decrease in the peripheral resistance occurs and the mechanism may be the local vasodilator effects of lowered oxygen tension. The increase in the cardiac output is felt to be a compensatory response to this decrease in peripheral resistance.(56)

In addition, in all the conditions accompanied by a high output there is an increase in the extracellular fluid volume. We perhaps do not need to postulate changes other than those already discussed under failure of the heart in the previous section. These changes undoubtedly do occur, and in the same manner, when the high output heart begins to decompensate. It seems to be established, however, that there is an increase in blood volume in these conditions somewhat earlier in the process.(45,48,56) That is, before the compensatory mechanisms have become inadequate, — with rising venous pressure and symptoms of congestion — the measured blood volume is found to be increased. Youman's suggests that this is due to a decreased blood supply to the kidney, secondary to the decreased peripheral resistance, with a consequent decrease in glomerular filtration rate. The amount of sodium chloride filtered is lowered and if there is no corresponding reduction in the rate of reabsorption by the renal tubules, salt and water are retained by the body. This process will be self-limiting if

the increase in blood volume so attained can raise the filling pressure to a degree that the further increase in cardiac output will produce a head of pressure at the kidney sufficient to again raise the renal blood flow and glomerular filtration rate to an adequate level. If this cannot be done — it becomes a self-perpetuating cycle and progressively more sodium and water are retained, raising the venous pressure still higher and dilating the already incompetent heart more and more.

ARTERIO-VENOUS FISTULA

The most instructive member of the high output failure family to analyze is arterio-venous fistula. The initial defect in the cardiovascular system is obvious, and, more important, the defect can be produced experimentally.

The first extensive experimental work on this entity was done by Emile Holman of John's Hopkins Hospital in 1923[21] and he at that time elucidated most of the acute and chronic changes seen.

For purposes of discussion the changes will be divided into those occurring immediately upon opening an A-V shunt, delayed effects of opening, the changes occurring immediately upon closure of the shunt and delayed effects of closure.

The immediate changes seen on establishment of an arterio-venous fistula may, I think, best be tabulated:

1. A fall in general arterial blood pressure affecting both diastolic and systolic levels.
2. An increase in pulse rate.
3. An increase in the cardiac output.
4. An increase in the pressure in the involved vein immediately proximal and distal to the fistula.
5. A decrease in the size of the heart.
6. A decrease in central venous pressure and in the right atrial pressure.[47,32,26]
7. Constriction of the systemic arterioles which shortly wears off.[47]

The reason for the fall in general arterial blood pressure is obvious when we visualize the sudden rapid run-off of blood from the arteries into the veins. The increased pulse rate is compensatory, probably

largely mediated by reflexes in the aortic arch and carotid sinus. Increased cardiac output has been discussed. The reason for increased pressure in the portion of vein surrounding the fistula is also obvious; however, it would seem that the right auricular and central venous pressure should also be increased by the sudden increment of arterial blood. It has been suggested that the reason this is not so is that the animal "bleeds" into the entire venous and capillary bed peripheral to the site of the shunt with a consequent pressure increase here and a decrease in central venous pressure and diastolic heart size.(9) The increase in pulse rate and cardiac output reflexly elicited from the fall in arterial blood pressure also contribute to a lowering of the venous pressure.(56)

The generalized constriction of the systemic arterioles is a reflex response triggered by the sino-aortic pressoreceptors which has a detrimental effect by decreasing flow elsewhere and increasing flow through the shunt. This vasoconstriction quickly wears off, probably because of the local vasodilator effects of lowered oxygen tension, increased CO_2 tension, and increased hydrogen ion concentration secondary to the decreased blood flow.(47)

The delayed effects of an arterio-venous fistula on the general circulation may also be tabulated:

1. An increase in blood volume of a degree roughly correlated with the size of the fistula.
2. Elevation of the venous pressure.
3. Enlargement of the heart (according to Holman - "due mainly to dilatation and only to a minor degree to hypertrophy").
4. A gradual recovery from the lowered blood pressure noted

immediately after the formation of the fistula, the systolic being equal to or higher, the diastolic definitely lower than that existing before formation of the fistula, thus producing a greatly increased pulse pressure.

5. A continued increase in the pulse rate.
6. A continued elevation of the cardiac output.
7. An increase in the pulmonary artery pressure.
8. An increased susceptibility of the animals to sub-acute bacterial endocarditis.

Theories as to a mechanism whereby the blood volume might be increased have been discussed in the previous section on high output failure. It has also been suggested that "at present it is only possible to say that some homeostatic mechanism involving the kidney, the liver and probably such endocrine organs as the pituitary and adrenal are concerned. In this connection it has been reported that the adrenal glands are enlarged in A-V fistula dogs."(26) In addition to the increase in blood volume there is an increase in the thiocyanate space. Since this is seen in the absence of obvious peripheral edema it is said to represent, in part, local edema near the sites of fistulas and, also, a diffuse increase in interstitial fluid insufficient to be evident as edema.

An elevation of venous pressure was not originally thought by Lewis and Drury to be present and because of this they felt that the cardiac output was not increased.(25) However, it should be recalled that mean pressure in the right auricle may not mirror end diastolic pressure in the right ventricle and that measured changes in pressure in atrium or ventricle may not accurately reflect changes in the length of the muscle fibres surrounding these chambers.(8) Because of the distensibility characteristics of the

great veins and the right auricle at the ranges of pressure studied an appreciable difference in the volume of blood contained in this system might not be detected from measurements of mean pressure. Most later investigators have found an elevation in venous pressure.(42, 9, 27)

That the cardiac output is not always elevated in small shunts has been shown by a couple of investigators.(44,10) In these cases circulatory adjustments might be accomplished by alterations in blood flow through other parts of the body.(7) It is known for example, that the flow of blood through uninvolved tubules and through the coronary bed may be reduced when an arterio-venous fistula is opened and increased when a fistula is compressed.

An increase in pulmonary artery pressure has been confirmed by several authors.(47,26,14) Gibbon and Churchill deduced a decline in pulmonary vascular bed resistance from their data and suggested a possible active change in the tone and calibre of the pulmonary vessels. Other workers disagree with this and state that it can be accounted for on the basis of increased cardiac output alone and that decreased pulmonary vascular resistance is due to mechanical distention of the blood vessels.(26)

Lillehei and his group observed that a large number of dogs with A-V fistulas developed sub-acute bacterial endocarditis originating both at the site of the fistula and on the valves of the heart.(27) This observation has since been confirmed and extended by other workers.(37) The possibility of developing endocarditis seems to be directly related to the size of the fistula, as well as to the age of the dog. Lillehei feels that his observation regarding adrenal gland enlargement may be linked to the change and that the inherent self-perpetuating characteristics of clinical endocarditis might be related to the adverse effects of cardiac stress upon the endocrine system affecting resistance to

infections.[27]

The acute effects of closing an arterio-venous fistula can be tabulated as follows:

1. Nicoladoni-Branham's sign — a sharp rise in blood pressure and a decrease in heart rate.
2. An increased heart size.
3. An increased central venous pressure followed by decrease in pressure.
5. A decrease in pulmonary artery pressure.

The rise in peripheral resistance produced by closing the shunt decreases the rate of run off of blood from the systemic arterial tree causing a rise in pressure. This increase is most pronounced in diastolic pressure and much less evident in systolic pressure. The pulse pressure is therefore narrowed. The form of the pulse wave is altered with the dicrotic notch appearing higher on the descending limb, presumably reflecting the increase in peripheral resistance. The pulse rate is slowed secondary to reflex stimulation of sino-aortic pressoreceptors.[56]

When an arterio-venous shunt is closed blood drains out of the vascular bed peripheral to the shunt, reducing the volume in the part and increasing the volume and pressure in the great veins and the cardiac chambers. This is a momentary thing but if it impinges upon an already overloaded heart the increase in pressure may be enough to result in decompensation and frank failure.

However, the pressure very rapidly decreases in the right auricle. Some writers do not believe this happens[5,51] which, once again, may result from the fact that the mean right atrial pressure does not necessarily reflect changes in the distension of the ventricular and atrial cavities.[9] Also reported is an acute decrease in pulmonary artery pressure.[27]

Three factors apparently contribute in varying degrees to the reduction in cardiac output: Firstly, the slowing of the cardiac rate; secondly, an increase in the pressure in the aorta against which the ventricle must develope its load and thirdly, a reduction in the input load with a decreased distension of the ventricles during diastole.(9)

A tabulation of the more remote effects of closure of an A-V fistula follows:

(a) A gradual readjustment of the blood pressure to a level seen before the creation of the fistula.

(b) Return of the pulse to a normal rate.

(c) Decrease in total blood volume.

(d) Decrease in the size of the heart.

The gradual readjustment of the pulse and blood pressure depends on a multitude of interrelated compensatory mechanisms.

The decrease in total blood volume is related to diuresis and to the development of a negative salt balance.(56) There does appear to be an increased renal excretion of sodium but there is no significant change in glomerular filtration rate, renal blood flow or renal venous pressure. Epstein suggests that sodium excretion may be conditioned by the degree of filling of the arterial tree.(8) At any rate it appears likely that the mechanism of unloading the excess extracellular fluid may not simply be the reverse of the mechanism for the retention of salt and water.

It should be mentioned that the recovery from the effects of an A-V fistula is, on closure of the defect, very rapid.

PART II

METHODS

METHODS

The principle purpose of our project was to be the study, in the condition of arterio-venous fistula, of changes, if any, in the intraventricular pressure on both the right and the left side of the heart. In addition, we felt that it would be valuable to obtain serial determinations of the peripheral blood pressure, cardiac output, blood volume, peripheral resistance and electrocardiographic and x-ray studies.

Preliminary Experimentation

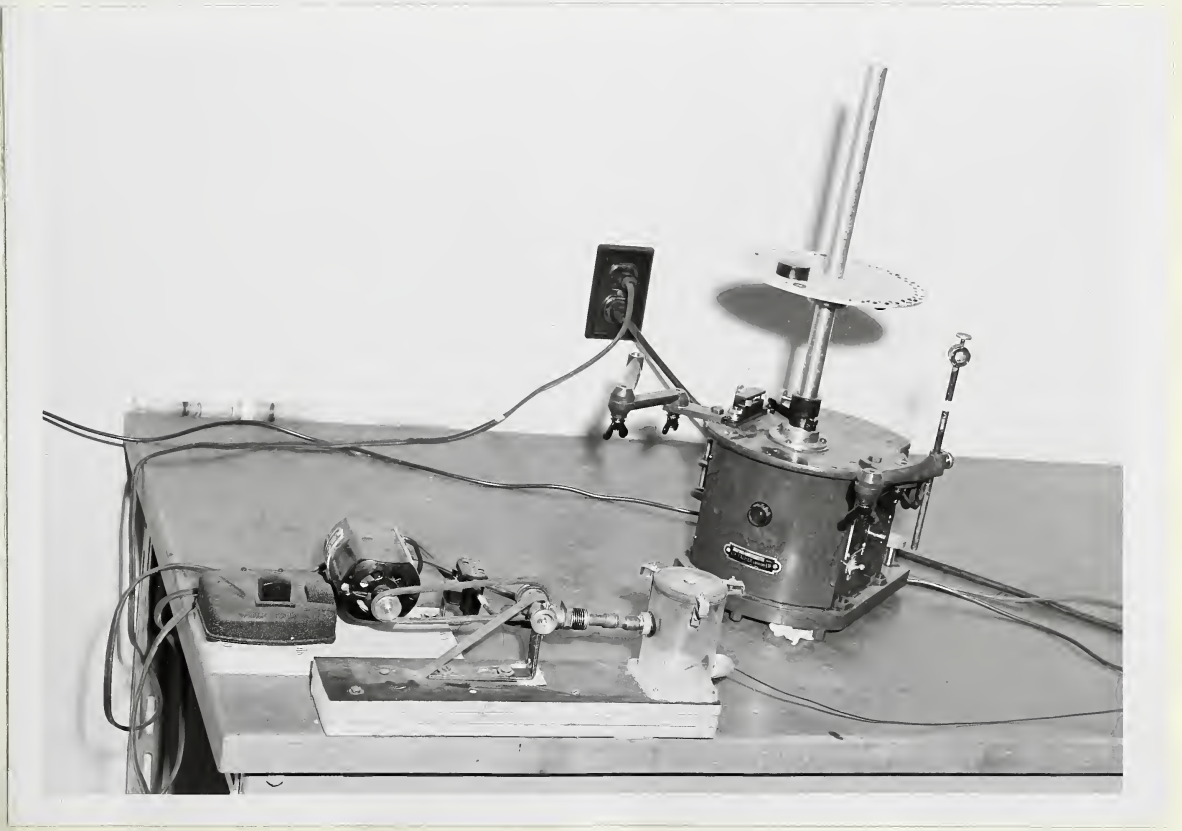
Pressure determination -- Our most pressing problem, and the one that proved to be the most difficult, was that of evolving a method for determining the pressure in the ventricular cavities. Our basic equipment was a Sanborn 4-channel polyviso recorder and two Statham strain gauge transducers.

The first thing to be done was to construct an apparatus for evaluating any recording system we might devise as to its frequency response. As stated by Wiggers(53) "distortion of ventricular pressure curves results from the use of inadequate manometer systems. Theoretic physical formulations and practical tests have demonstrated that reliable curves can be recorded only by a manometer system which has an adequate frequency and proper damping characteristics expressed by the logarithmic decrement of its free vibrations." Wiggers is convinced that for a recording system to be accurate it should reproduce not only the natural frequency of the wave to be recorded but up to the tenth harmonic of the natural frequency.

The apparatus which we used for evaluating these responses consisted of a cylindrical glass chamber mounted on a plastic base and partially filled with water. The glass was suaged to the plastic base with acetyl acetate which rendered the plastic sticky and cohesive. A

glass top fitted with a rubber washer could be tightened into place with a number of brass set screws. A hole in one side of the cylinder, one inch from the bottom, served for the introduction of needles and catheters, which could be then made airtight by means of plasticine. On the other side of the cylinder, three inches from the top, was another opening to a small piston which was driven by a pully attached to a sewing machine motor. By means of a variable rheostat the motor could be made to drive the piston at varying speeds which would inscribe sine waves into the recording system at corresponding rates.

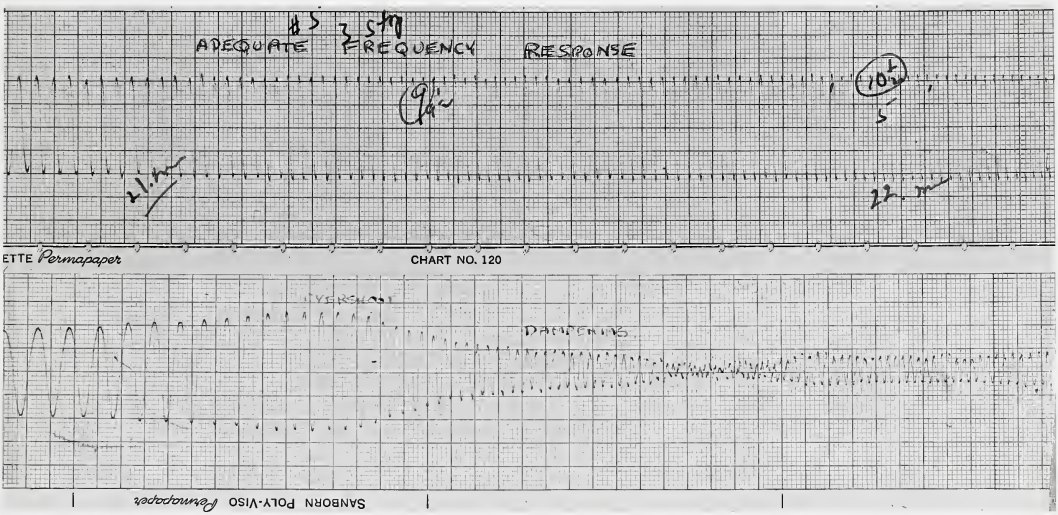
Fig. 1 - Photograph of Apparatus
for Testing Frequency Response.



EXAMPLE OF ADEQUATE AND

OF INADEQUATE FREQUENCY RESPONSE

USING TESTING DEVICE.



Our initial attempts to obtain right ventricular pressures were through a PE-90 polyethylene catheter (inside diameter 0.86 mm., outside diameter 1.27 mm.) attached to a polyethylene to Luer-Lok coupler (A-2625B) which was passed through a thin-walled #18 needle and into the external jugular vein. A 15 cm. length of this catheter gave a satisfactory frequency response on our testing apparatus. With a longer length of tubing, however, damping was found to be excessive. Since the fine catheter was difficult to manipulate, impossible to see on x-ray and a longer piece would be required to consistently penetrate the right ventricle, this method was abandoned.

Next, a PE-240 polyethylene catheter (inside diameter 1.67 mm., outside diameter 2.42 mm.), into one end of which was inserted the hub and a short length of a #13 needle, was introduced into the external jugular vein, threaded down into the right atrium, and tied into place. The proximal end of the catheter was advanced around the lateral side of the neck in a subcutaneous skin tunnel and the needle hub was brought through the skin and attached to a B.D. one-way valve (No. 3410V) which was in turn secured to the mid-line posteriorly of the dog's neck by means of a pocket in a cloth and tape collar. The system was filled with a heparinized saline solution and left in place. We hoped that dye for measuring cardiac outputs and blood volumes could be injected through the one-way valve, and that the valve could be removed and a #14 cardiac catheter passed through the needle and polyethylene tubing for pressure determination. On two dogs the apparatus was in place for eight days and eleven days respectively and was patent for withdrawal for four and six days respectively. In each dog, material could be injected at all times while the catheters were in place. On examination at the end of the eight and eleven day periods both right atria were found to be almost completely filled with adhesive friable

clot which in each case extended up into the superior vena cava. The catheters in both dogs remained free of clot and it was obvious that clot at the end of the catheter formed a flap-valve arrangement which permitted the egress of fluid but did not allow withdrawal.

A #16 thin-walled needle was next introduced into the external jugular vein and through this a #4 cardiac catheter was threaded. In two dogs, at this time, skin tubes were constructed which we felt might facilitate the puncture of the veins but in a short time a fibrous reaction closed the veins off and the tubes became necrotic and eventually disappeared. However, we found the veins could be fairly consistantly punctured without this aid and recorded a number of right ventricular pressures using this system. Due to an oversight we had not tested the frequency response of the catheter. It was sold commercially for the recording of intracardiac pressures and we assumed the frequency response should be adequate. On testing, however, we found that it was not; and also that the low pressure strain gauge through which we were recording gave a poor response. This system (P-23B -- pressure transducer -- 0-5 cm. Hg) was also abandoned.

Our first attempts to obtain left ventricular pressures were by passing PE-90 polyethylene catheters similar to the ones used initially on the right side through #18 thin-walled needles and in a retrograde manner down the carotid arteries and through the aortic valve. (The carotid arteries had previously been transplanted subcutaneously). This was found to be impossible.

We next used a PE-240 polyethylene catheter prepared as previously described for the right side of the heart with a #13 needle and one-way valve. The catheter was tied into the carotid artery and advanced down to the ascending aorta, while its proximal end was brought around the side of the neck and out in the mid-line as before. Here as on the right side the

catheter remained patent, but on post-mortem the aorta was found to be almost occluded by masses of clot.

As we had recently started recording pressures from the left atria of patients by means of puncturing the left main bronchus through a bronchoscope, an attempt was made to record pressures from the dog in this manner but it was found to be very awkward and the pressures obtained were completely unsatisfactory.(1)

Bjork's method of recording left ventricular pressure in humans by means of needle puncture of the back suggested a direct approach with a needle through the intact chest wall.(3)

In the first dog on whom this method was tried, a tracing was obtained but the dog almost immediately developed ventricular fibrillation and died. At post-mortem it was found that the needle had penetrated the anterior descending branch of the left coronary artery.

Peripheral Blood Pressure -- Our first recordings of peripheral blood pressure were made with a #20 needle in a previously transplanted carotid artery. The needle recorded accurately when attached to a 13 cm. length of PE-130 polyethylene tubing. We were unable, however, to get a sufficient flow of blood for our cardiac output determinations through this size of needle. When a larger needle was substituted we found that, in addition to the difficulty of puncturing the mobile artery, we had trouble controlling hemorrhage when the needle was withdrawn.

Cardiac Outputs -- These were to be determined by the method employing Evan's blue T1824 dye. The validity of this method has been questioned(35) but the most recent consensus of opinion seems to be that it is completely valid, and in fact, probably the most accurate available method.(6, 52,42)

Our first output determinations were done by the technique of

multiple sample collection. 6.25 mgm. of Evan's blue dye was injected from a calibrated syringe, through a #4 cardiac catheter, into the right ventricle. An 18 cm. length of PE-240 polyethylene catheter used for recording peripheral pressures was attached to a collecting needle and arterial blood was collected in heparinized tubes mounted on a kymograph machine which rotated at a speed of 1.3 cm. per second beneath the collecting needle. The tubes were spun down in a centrifuge and the plasma was transferred to 3 c.c. volumetric flasks by means of a micropipette. The plasma was diluted 30 times with distilled water and readings were made on a Beckman machine, and later, when the proper filters were obtained, on an Evelyn galvanometer using Hellige tubes in the microadaptor.

From the density readings obtained the dye concentration in each sample could be calculated using a previously constructed calibration curve. These readings were plotted on semi-logarithmic paper and the descending limb of the dye curve extrapolated to the base line following Hamilton's technique.(16)

The curve was then replotted on linear graph paper and the area under the curve was calculated. To do this a 10 cm. square of paper and the curve were cut out of the same piece of paper and weighed. The ratio $\frac{\text{wt. of curve}}{\text{wt. of 100 cm.sq.}} \times 100$ gave the area of the curve in square centimeters. This area divided by the base line of the curve gave the height in centimeters of a line representing the mean concentration. From this the cardiac output in terms of litres of plasma per minute could be calculated by formula. A hematocrit correction gave the output in terms of whole blood flow. The method proved satisfactory but was cumbersome and was liable to many sources of human error.

Blood Volumes — These were originally calculated using a three sample

collection method at 10, 20 and 30 minutes. 6.25 mgm. (the dye injected for the cardiac output) plus 2.5 mgm. (the residual dye in the catheter and stopcock) gave a total of 8.75 mgm. as the original delivered dye. The galvanometer readings obtained on the three plasma samples were extrapolated back to 0 time where there was presumably instantaneous mixing. A value for plasma volume was obtained and a hematocrit correction enabled us to transpose it to blood volume.(17)

Electrocardiogram — We at first tried using the conventional electrocardiogram electrodes which were found to give very poor recordings. Needles were then mounted on brass fittings which screwed onto the electrodes. This system produced satisfactory tracings. With the electrodes in the conventional places, however, a tracing was obtained which was in no way comparable to a human electrocardiogram.

X-rays — X-rays were found to be relatively satisfactory. An attempt was made to construct a fluoroscopic table to enable us to pass the catheters under direct vision but this apparatus still requires some modification.

TECHNIQUE

1. Subjects.

Mongrel dogs weighing from 9 to 25 kilograms were used. The first eight dogs operated on were given courses of distemper vaccine and were treated to rid them of worms. These dogs had also been acclimatized to the laboratory. Later, however, it was found to be impossible to follow this procedure as there was no reservoir of animals and several investigators were competing for the insufficient number of dogs that were obtained. Two dogs did succumb to distemper and four to some mysterious upper respiratory infection which affected a number of the laboratory animals, and for which no cause was found. Dogs were fed on a mash obtained from a flour mill which contained, besides various cereals, meat meal, fish meal, bone meal, brewers yeast, fish oil, wheat germ, powdered milk, salt and potassium iodide.

2. Anaesthesia.

For all operative procedures and for the pressure and cardiac output determinations, the dogs were anaesthetized with intravenous nembutal given in a dosage of 35 mgm. per kilogram of body weight. Originally, intravenous pentothal was used, but this was found to be unsatisfactory because of its short action. There were two anaesthetic deaths with this drug. Nembutal was found to be better and although there were four deaths, this number was in a much larger total number of anaesthetics. On a few occasions the calculated dose of nembutal was given intraperitoneally with satisfactory results.

For procedures in which the thoracic cavity was opened a positive pressure respirator was necessary. The mine Safety Appliance "Pneophore" combined with an inflatable endotracheal tube worked well except for two occasions in which the outlet valve stuck and resulted in deaths of dogs.

OPERATIVE PROCEDURES

a. Carotid Transplant and Cardiopexy

To overcome the previously mentioned difficulty of puncturing to carotid artery consistently and of stopping the bleeding after it had been done with a large needle, we decided to bring the carotid artery out into a skin tube.

The neck was shaved, painted with iodine and an incision made one-half inch medial to the left external jugular vein. The strap muscles were split and the carotid artery isolated from the other structures in the carotid sheath. An incision was then made parallel and about one-half inch lateral to the original one and the resulting flap cleaned of subcutaneous fat. The artery was brought up and the skin flap was sutured, using interrupted 30 silk, to form a tube around the artery. The defect in the skin beneath the newly constituted tube was then closed in the same way. We found that tubes made too tight about the vessel tended to thrombose the artery and then slough out.

Because of our inability to accurately position a needle through the closed chest wall and because of the difficulty of consistently hitting a relatively mobile heart, we decided to affix the left ventricle to the anterior chest wall.[11]

A horizontal incision was made over the shaved, painted chest — starting at the left sternal border in the 4th interspace and extending to the anterior axillary line. The intercostal muscles were divided and the periosteum was stripped from the 4th rib, which was then removed along with its costal cartilage. In selected instances the 3rd and/or 5th ribs were also removed. The heart in its pericardial sac was dislocated manually from its diaphragmatic attachment and three sutures (30 silk) were placed through the left ventricular wall at the apex of the heart in a triangular fashion,

using as a guide, the obvious anterior descending branch of the left coronary artery. The pericardium was not opened. There was usually a minimal amount of bleeding. The apex of the heart was then affixed to the anterior chest muscles and the thorax was closed using interrupted cotton for the pleural, muscular and subcutaneous layers and catgut for skin. Subsequent experience has shown that silk appears to give a fair amount of postoperative reaction and we are now using nylon for the ventriculopexy.

b. Arterio-Venous Fistula.

Our first two unsuccessful attempts to perform this operation were through vertical supra pubic incisions as suggested by Markowitz.[28] For us, this incision gave very poor exposure. A transverse incision was subsequently made about two inches below the umbilicus, and all muscle layers were divided. The abdominal viscera were displaced and packed with saline cloths and the inferior vena cava and abdominal aorta dissected free for two to three inches above the aortic trifurcation. The adventitia was then carefully stripped from the aorta and to a lesser degree from the inferior vena cava. The two vessels together were brought up into a Smith-Freeman arterial clamp which was tightened down to leave a portion of each vessel in continuity behind the clamp. Parallel openings were then made in the two vessels for the length of the anticipated fistula. Two stay sutures were placed at each end of the opening and the posterior layer of the fistulous opening was closed -- using the long end of one stay suture and a continuous over and over stitch. This was tied to the other stay suture and brought back to close the anterior layer. 5-0 surgilon was used for closure and was found to be more satisfactory than 5-0 arterial silk. Reports in the literature[26,27,47] indicated that 1 to 2 cm. was probably the optimal size for the defect. In our experience fistulas much larger

than 12 mm. tended to produce failure too rapidly. A recent report (37) indicates that fistulas under 1 cm. in size thrombose off and we have had this happen in one dog. The abdomen was closed with catgut and interrupted cotton.

Post-Operative Care

All animals received injections of SR-penicillin 400,000 units at the time of each operative procedure and also at the time pressures and cardiac outputs were determined. After fistulas were established, because of the the high incidence of subacute bacterial endocarditis in such animals most animals were given the penicillin every two or three days. A quantity of long-acting penicillin ("Bicillin") was used at weekly intervals for this prophylactic purpose for as long as a donated supply lasted.

Pressure Determinations

Dogs were anaesthetized in the usual manner and tied on a dog board with the head over one end. An electrocardiogram was taken immediately because we found that later in the procedure when the dogs became more nearly awake muscular tremors tended to spoil the records. To obtain cardiograms that were comparable to human ones, we placed the left leg lead in the right leg, the right leg lead in the left leg, the left arm lead in the left axilla and the right arm lead between the scapulae. Leads I, II, III, AVR, AVL and AVF were taken.

Puncture of the right external jugular vein was then made using a #15 thin-walled needle. Through this needle a #5, 3-hole cardiac catheter was threaded and passed on into the heart. The catheter was attached to a 3-way stopcock, into one outlet of which was plugged intravenous tubing leading from a suspended bottle of 5% glucose in N/S. The other outlet of the stopcock could be attached to a strain gauge for recording pressures.

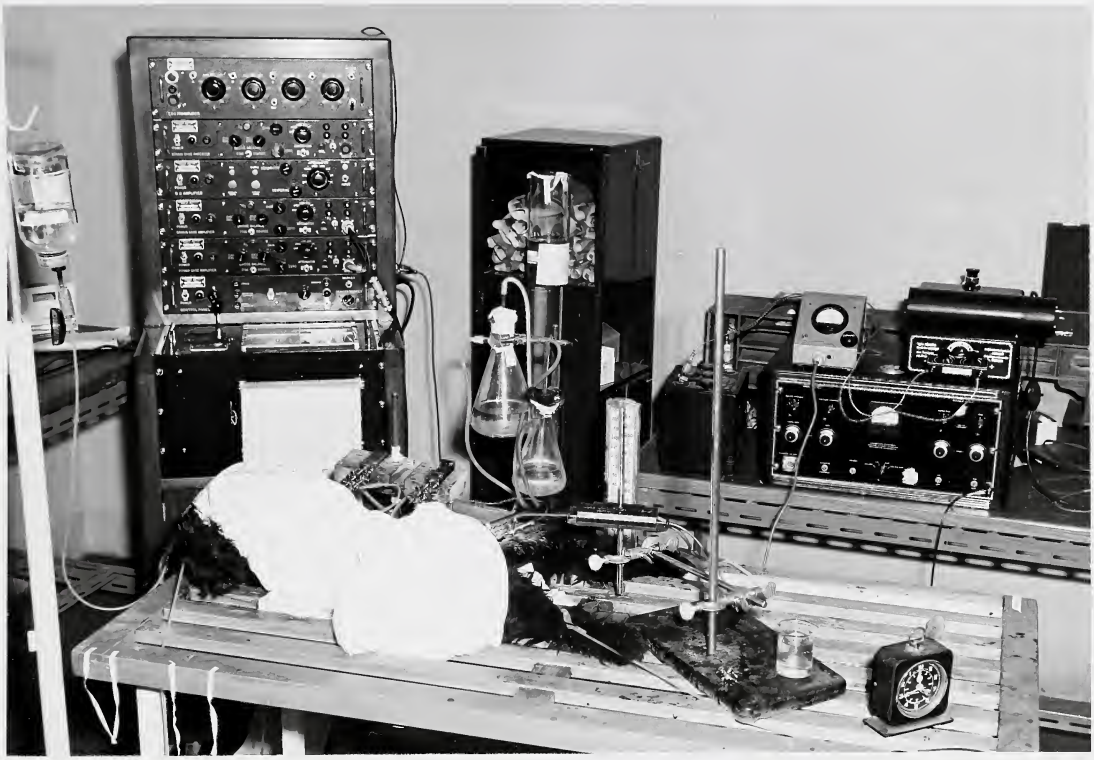
With the pressure recording the catheter was then passed blindly into the right ventricle by constantly monitering on the Sanborn machine. When the catheter tip reached the ventricle the stopcock was turned allowing the saline to drip through the catheter to obviate plugging. We did not find it necessary to heparinize this solution. (In one dog an unfortunate death resulted when by mistake a solution of 5% KCl was added to keep the catheter open. The dog developed an arrythmia and when we managed to get a terminal electrocardiogram, it showed the typical configuration of hyperpotassemia).

A #18 thin-walled needle containing a stilette was then passed into the exteriorized carotid artery. The stilette was rapidly removed and a 3-way stopcock placed on the needle, which was taped into place. One outlet of the stopcock was joined by an 18 cm. length of PE-240 polyethylene tubing to the strain gauge for recording. Polyethylene to Luer-Lok couplers (A-2625-D), (Clay-Adams Co.) were used on both ends of the catheter. This piece of catheter had been previously tested on our machine and gave an adequate frequency response through a #18 needle.

The other outlet of the stopcock led to a Wood's oximeter cuvette (Model XC-50B- The Waters Corporation).

Our two strain gauges were set up on a holder as shown. Fig. 2, and Fig. 3.

Fig. 2.

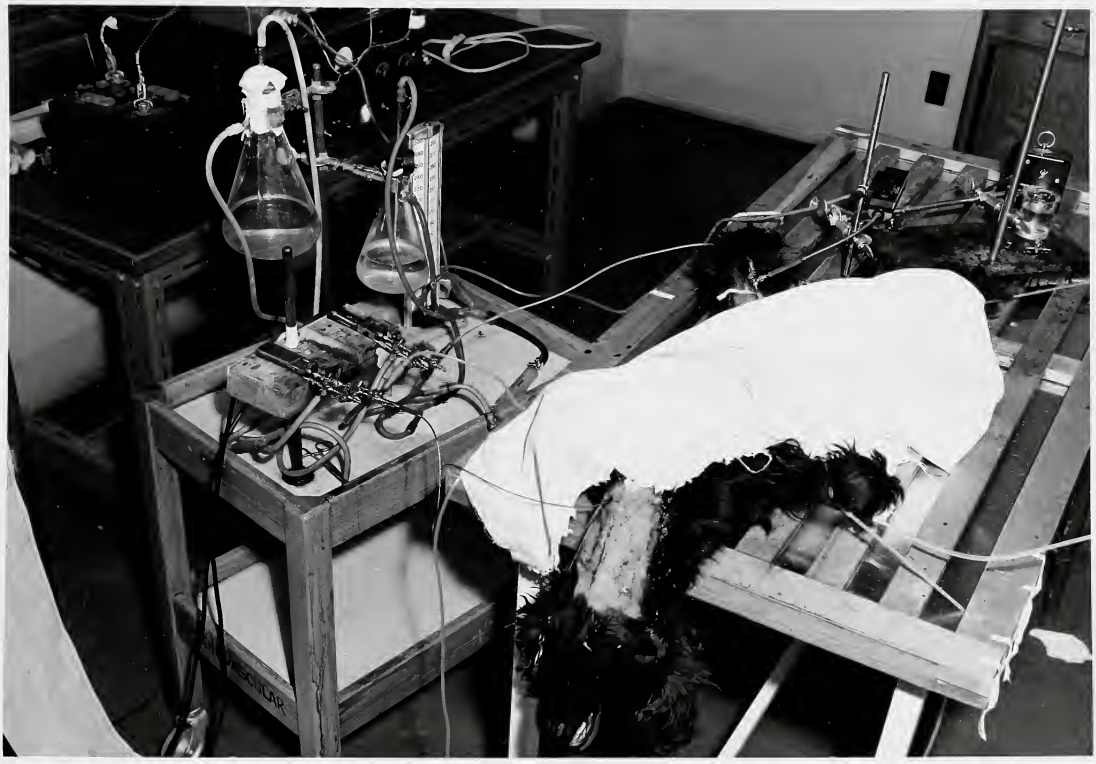


Photograph of Apparatus

as used for

Hemodynamic Measurements.

Fig. 3.



Close-up of Apparatus

as used for

Hemodynamic Measurements

A mercury manometer could be converted at will to either a reservoir which was placed at the level of the right atrium or to a second bottle containing a solution of heparinized saline. By turning the appropriate stopcocks this could be used for either flushing out the recording system (by means of the pressure bottle) or for calibrating the pressure waves already recorded (by applying known pressure to the balance bottle).

An attempt was usually made to record pulmonary artery pressure but when this was not easily obtained we did not persist. The catheter was barely pulled out of the right ventricle to record our right auricular pressures.

When the carotid artery pressure had been recorded the polyethylene catheter was disengaged from the 3-way stopcock and a #21 needle attached to its end. With a continuous flow of heparinized saline flushing through from the pressure bottle, the needle was easily introduced through the chest wall into the previously affixed left ventricle. On a few occasions we used an extra strain gauge and an identical piece of tubing to get simultaneous carotid, and right and left ventricular pressures.

Oxygen Saturations.

With the catheter back in place, blood from the carotid artery was withdrawn through the Wood's cuvette in the conventional manner for the determination of oxygen saturation. The principle on which this instrument works depends on the relative difference in transmission of light in the red range (620 u) and the infra-red range (800 u) through reduced hemoglobin and oxyhemoglobin[55,48] Using the single-scale galvanometer, as we did, the galvanometer deflection, after some initial settings, is a function of the oxygen saturation and this can be read directly off a graduated scale.

Using the same initial settings, the cuvette was then attached

to the 3-way stopcock on the catheter into the right ventricle and blood withdrawn for a right ventricular oxygen saturation.

Cardiac Output

Our final apparatus for recording cardiac output consisted of a recording camera with a galvanometer light beam which was actuated by the photo cells in the Wood's oximeter cuvette. The camera was a German one which we modified by adding two lights flashing periodically to give time lines on our completed tracings. It could be attached to the control box for the Wood's cuvette. By a process of trial and error we found that our maximum sensitivity was at a voltage of 5 with the red and the infra-red controls both set at 10.

Prior to the actual output determination, 22 cc. of blood was withdrawn through the cuvette into a heparinized syringe for calibration purposes. While this withdrawal was taking place the galvanometer beam in the camera was set at approximately 20 (near the bottom of the scale) and a base line was run around the paper. The blood withdrawn was placed in 4 - 5 c.c. volumetric flasks. One sample served as a control and to the others were added 50 gamma, 100 gamma, and 200 gamma of Evan's blue dye respectively. An "Agla" micrometer syringe (Burroughs Wellcome) was used for this purpose. This gave concentrations of 0, 10, 20 and 40 mgm. of Evan's blue dye per litre.

The catheter to the right ventricle was disengaged from the strain gauge (after checking to see that it was still in right ventricle) and a syringe calibrated to deliver 7.9 mgm. of T1824 dye was attached to the 3-way stopcock. The carotid artery stopcock was turned to flush blood through the cuvette and withdrawal was started. As soon as the base-line appeared steady on the cuvette the dye was injected into the right ventricle. At the same

instant the camera was started. An adequate curve was usually obvious to the operator on the camera because of the light beam fluctuation. As soon as the curve was completed, the camera was stopped and the blood withdrawn through the cuvette was pushed back into the animal. Immediately following the injection the stopcock on the catheter was also turned into the animal to flush the residual dye in catheter and stopcock.

The four specimens of blood of known dye concentration were next pulled through the cuvette and each one was recorded on the camera as it came through. This blood was then discarded.

When the film was developed a dye curve could be seen with an obvious late ascending limb, representing recirculation. Following Hamilton's method the points of the descending limb of the dye curve were plotted on semilogarithmic paper and extrapolated to a base line. The points obtained by extrapolation were replotted onto our original curve. The area under this curve was calculated, using the same method of weighing paper that we had used in the multiple sample method, and the mean concentration determined. Its absolute value in terms of dye per litre was obtained from the calibration lines which appeared on the same tracing. From this, by formula, the cardiac output in terms of litres of blood per minute could be calculated.

Blood Volume

At the instant that the dye for the cardiac output was injected into the right ventricle a time clock was set for ten minutes. At the end of this interval and at the end of 20 and 30 minutes from the original injection time, samples of blood were withdrawn through the Wood's cuvette and the galvanometer deflections resulting were recorded on the camera. From these recorded galvanometer deflections concentrations in terms of milligrams of dye per litre could be read and these values extrapolated

back to 0 time. From this 0 time concentration the blood volumes were calculated. The amount of dye to be used in this calculation was that delivered for the cardiac output (7.9 mgm.) plus that remaining in the catheter and stopcock (3.0 mgm.). Blood volume in litres was therefore $\frac{10.9 \text{ mgm.}}{\text{Conc. of dye at 0 time in mgm./litre.}}$

Here again a hematocrit correction was not necessary.

Chest x-rays

Following these determinations the dog was moved from the table into another room containing the x-ray machine. Settings used were MA — 25, KVP — 68 on 15 high.

Distance used was 30" from aperture to casette.

Following the determinations the catheters and needles were removed. To stop persistant bleeding from the carotid artery puncture it was found necessary to apply an intestinal clamp lightly lengthwise along the vessel for from 15 minutes to 3 hours.

PART III

RESULTS

RESULTS - 3 Series

SERIES A

DOGS NEVER REACHING THE A-V FISTULA STAGE

Dog #6 B -- 12 kilograms.

September 23rd, 1954 -- carotid transplant.

October 20th, 1954 -- Anaesthetized for output determinations. Attempt made to insert needle through anterior chest wall into left ventricle. Ventricular fibrillation. Defibrillated with electrical defibrillator. Cardiac massage. Death.

Post-mortem examination -- needle-hole through anterior descending branch of left coronary artery.

Dog #2 C -- 15 kilograms

September 30th, 1954 -- PE-240 catheter attached by a #13 needle to one-way valve inserted into external jugular vein and threaded into right atrium. Proximal end brought around to back of neck via skin tunnel.

October 3rd, 1954 -- polyethylene catheter still patent for withdrawal.

October 4th, 1954 -- catheter no longer patent.

October 8th, 1954 -- dog died.

Post-mortem examination -- large friable clot in right auricle extending up into superior vena cava forming flap valve arrangement over end of catheter.

Dog #2 D -- 13 kilograms

October 1st, 1954 -- PE-240 catheter attached by means of #13 needle to one-way valve inserted into left external jugular vein and threaded

down into the right auricle. Similar catheter inserted into right carotid artery and advanced to the aortic valve. Both catheters brought around to the posterior neck via skin tunnels.

October 7th, 1954 -- both catheters have closed off for withdrawal.

October 12th, 1954 -- dog died.

Post-mortem examination -- right auricle filled with clot as described above for Dog #2 C. Clot of similar character in arch of aorta surrounding catheter in place there.

Dog #1 B -- 11 kilograms

October 6th, 1954 -- PE-240 catheter attached by means of #13 needle to one-way valve inserted in carotid artery and advanced to arch of aorta. Brought around to posterior neck vein skin tunnel.

October 13th, 1954 -- dog died.

Post-mortem examination -- arch of aorta filled with clot.

Dog #1 D -- 25 kilograms

November 13th, 1954 -- Dog anaesthetized with pentothal prior to carotid transplant. Anaesthetic death. Cardiac massage unsuccessful.

Post-mortem examination -- not done.

Dog #6 -- 14 kilograms

December 16th, 1954 -- cardiopexy and carotid transplant.

December 24th, 1954 -- coughing, appeared feverish, dehydrated. Started on intravenous therapy.

December 28th, 1954 -- Anaesthetized prior to base-line determinations of cardiac output etc. Was struggling and anaesthetic given faster than usual. Anaesthetic death. Positive pressure breather and cardiac massage to no avail.

Post-mortem examination -- negative.

Dog #8 -- 11 kilograms

December 27th, 1954 -- cardiopexy and carotid transplant.

January 12th, 1955 -- base-line cardiac output and pressure determinations.

February 3rd, 1955 -- anaesthetized prior to A-V fistula operation. Anaesthetic death.

Post-mortem examination - cardiopexy examined and no gross or microscopic evidence of fibrosis or necrosis about ventricular sutures.

Dog #3 B -- 13 kilograms.

January 10th, 1955 -- carotid transplant and cardiopexy.

January 24th, 1955 -- coughing, profuse mucoid discharge from upper respiratory passages. Intravenous therapy commenced.

February 11th, 1955 -- dog died.

Post-mortem examination -- patchy atelectasis, both lungs. Some patchy pneumonic consolidation, right base.

Dog #2 B -- 20 kilograms.

January 14th, 1955 -- carotid transplant and cardiopexy.

January 26th, 1955 -- discharge from nose and mouth, coughing. Intravenous therapy, antibiotic treatment commenced.

February 3rd, 1955 -- dog died.

Post-mortem examination -- negative.

Dog #3 D -- 13 kilograms

January 22nd, 1955 -- dog anaesthetized for carotid transplant and cardiopexy. Carotid transplant performed.

Just after chest opened for cardiopexy positive pressure breather

stopped. Dog died of asphyxia before "Pneophore" could be corrected or chest closed.

Post-mortem examination -- not done.

Dog #1 C -- 13 kilograms.

February 13th, 1955 -- carotid transplant and cardiopexy.

February 25th, 1955 -- anaesthetized for base line cardiac output and pressure determinations. 500 c.c. bottle of potassium chloride attached to catheter in right ventricle. Dog died of hyperpotassemia, (electrocardiographic evidence).

Post-mortem examination -- negative.

Dog #3 c -- 13 kilograms

February 23rd, 1955 -- carotid transplant and cardiopexy.

March 1st, 1955 -- mucoid discharge from nose and eyes. Treatment started.

March 8th, 1955 -- dog died.

Post-mortem examination -- negative.

SERIES B

DOGS REACHING A-V FISTULA STAGE -- NO FOLLOW-UP

Dog #5 -- 10 kilograms

December 2nd, 1954 -- carotid transplant and cardiopexy.

December 20th, 1954 -- cardiac output -- 1.92 litres/min. pressure recordings -- lost.

April 6th, 1955 -- arterio-venous fistula 0.9 cm. in length.

April 18th, 1955 -- anaesthetized - struggling - I.V. nembutal given quickly. Dog died of anaesthetic.

Post-mortem examination -- negative.

Dog #2 -- 24 kilograms

September 20th, 1954 -- carotid transplant.

October 19th, 1954 -- cardiac output - 1.5 litres/min.

Pressures -- carotid - $\frac{209.4}{162.4}$, mean - 184.8

December 1st, 1954 -- cardiopexy.

December 21st, 1954 -- cardiac output 1.72 litres/min. Blood volume -- 0.91 litres. Pressures -- R.V. $\frac{28.4}{22.6}$ mean 25.5 (probably PA)

L.V. $\frac{180.5}{0}$ mean 66.0

Carotid $\frac{205.3}{130.6}$ mean 164.0

January 14th, 1955 -- A-V fistula 2.0 cm. in length. Dog died in eight hours.

Post-mortem examination -- acute pulmonary edema, moderate dilatation of left ventricle.

Dog #1 -- 10 kilograms

December 2nd, 1954 -- cardiac output - 0.69 litres/min.

Blood volume -- 0.47 litres.

Pressures -- R.V. - $\frac{23.6}{0}$, mean 11.4

L.V. - $\frac{165.1}{0}$, mean 66.0

Carotid - $\frac{185.0}{122.5}$, mean 145.0

P.A. - $\frac{22.3}{19.1}$ mean 20.8

January 16th, 1955 -- A-V fistula 0.75 cm. in length.

January 20th, 1955 -- dog died. Cause unknown.

Post-mortem examination -- negative.

Dog #3 -- 20 kilograms

December 8th, 1954 -- carotid transplant and cardiopexy.

December 23rd, 1954 -- cardiac output 2.6 litres/min. Blood volume 1.4 litres. Pressures -- R.V. $\frac{17.0}{0}$ Mean 8.6

L.V. $\frac{140.5}{0}$ Mean 64.0

Carotid $\frac{155.0}{110.0}$ Mean 125.0

January 6th, 1955-- Vertical suprapubic incision. A-V fistula 1.3 cm. in length. Profuse bleeding from anastomatic line when clamp removed. Packed with gelfoam and closed.

January 7th, 1955 -- dog died.

Post-mortem examination -- massive secondary hemorrhage from fistula site.

Dog #6 C -- 8 kilograms

January 17th, 1955 -- carotid transplant and cardiopexy.

February 11th, 1955 -- cardiac output 0.41 litres/min.

Pressures -- R.V. $\frac{12.6}{0}$ mean 8.1

L.V. $\frac{175.0}{0}$ mean 65.0

Carotid $\frac{175.6}{135.0}$ mean 160.0

March 22nd, 1955 -- A-V fistula, 1.5 cm. in length. (Hematocrit prior to this procedure - 36).

March 26th, 1955 -- dog died.

Post-mortem examination -- patchy atelectasis, both lungs. Otherwise negative.

Dog #1 B -- 12 kilograms

January 31st, 1955 -- carotid transplant and cardiopexy.

February 13th, 1955 -- cardiac output 1.2 litres/minute.

Pressures -- R.V. $\frac{17.2}{0}$ mean 8.8

L.V. $\frac{58.6}{0}$ mean $\underline{107.1}$

Carotid $\frac{173.8}{102.6}$ mean 51.0

March 18th, 1955 -- A-V fistula 1.0 cm. in length.

March 20th, 1955 -- dog died.

Post-mortem examination -- negative.

Dog #8 B -- 17 kilograms

February 7th, 1955 -- carotid transplant and cardiopexy.

March 14th, 1955 -- cardiac output 2.1 litres/minute.

Pressures -- R.V. $\frac{31.7}{0}$ mean 10.6

L.V. $\frac{120.0}{0}$ mean 63.0

Carotid $\frac{128.0}{100.9}$ mean 116.0

April 7th, 1955 -- R.V. $\frac{18.2}{0}$ mean 9.1

L.V. $\frac{133.0}{0}$ Mean 57.0

Carotid $\frac{136.8}{91.2}$ mean 110.2

April 10th, 1955 - A-V fistula 2.2cm. in length.

April 18th, 1955 -- dog died. Acute pulmonary edema, left ventricle dilated. Heart failure cells in lungs.

Post-mortem examination -- acute pulmonary edema, left ventricle

dilated. Heart failure cells in lungs.

Dog #10 — 9 kilograms

April 18th, 1955 — carotid transplant and cardiopexy.

May 5th, 1955 — cardiac output 1.97 litres/minute. Blood volume 0.70 litres. Per resistance 4.26 units.

Pressures — R.V. $\frac{31.5}{0}$ mean 12.6

L.V. $\frac{155.0}{0}$ mean 95.0

Carotid $\frac{155.0}{125.0}$ mean 140

May 9th, 1955 — A-V fistula 1 cm. in length.

May 13th, 1955 — cardiac output 0.98 litres/minute. Blood volume 0.53 litres. Peripheral resistance 4.55 units.

Pressures — R.V. $\frac{28.0}{0}$ mean 9.8

L.V. $\frac{112.5}{2.5}$ mean 45.0

Carotid $\frac{100.0}{49.5}$ mean 74.3

May 18th, 1955 — Dehiscence of abdominal wound. Given nembutal 25 mgm/kilogram for resuturing. Anaesthetic death.

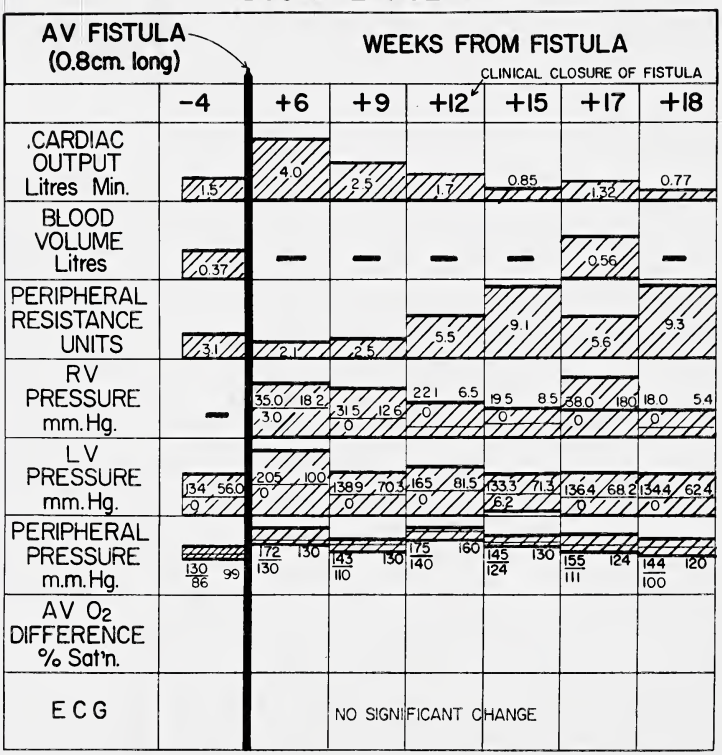
Post-mortem examination — heart failure cells in lungs.

SERIES C — Dogs reaching A-V fistula stage on whom hemodynamic measurements were carried out.

DOG 7. FEMALE 10 KILOS.

AV FISTULA (1cm. long) →	Weeks from establishment of A V Fistula								
	−2	+3	+7	+9	+12	+14	+16	+17	+21
CARDIAC OUTPUT Litres Min.	3.2	2.71	3.05	3.15	3.86	3.27	3.75	2.34	1.99
BLOOD VOLUME Litres	0.49	0.71	—	—	—	—	—	0.64	—
PERIPHERAL RESISTANCE Units	5.4	3.8	—	3.0	3.12	3.07	2.63	3.87	4.3
R.V. PRESSURE mm. Hg.	14.6 / 0 82	178 / 0 9.0	—	23.4 / 0 9.8	19.5 / 0 8.9	30.0 / 0 24.0	29.8 / 0 10.8	36.1 / 0 14.5	39.6 / 0 15.6
L.V. PRESSURE mm. Hg.	20.6 / 0 9.3	195 / 0 95	—	157 / 0 74.2	130 / 0 39.6	204 / 0 80.6	223 / 0 108.5	198 / 0 97.2	135 / 0 72.0
PERIPHERAL BLOOD PRESSURE mm. Hg	210 195 175	205 170 145	—	202 157 121	196 129 110	217 167 124	248 164 131	199 151 108	192 143 120
AV O_2 DIFFERENCE % Sat'n.	—	—	—	—	—	—	—	78–66 / 12%	88–68 / 20%
P.A. PRESSURE mm. Hg.	—	—	—	—	—	45 / 29 / 27	27.6 / 19.8	28.1 / 19.1 / 14.7	30.0 / 23.6 / 18.7
E.C.G.	NO SIGNIFICANT CHANGE								

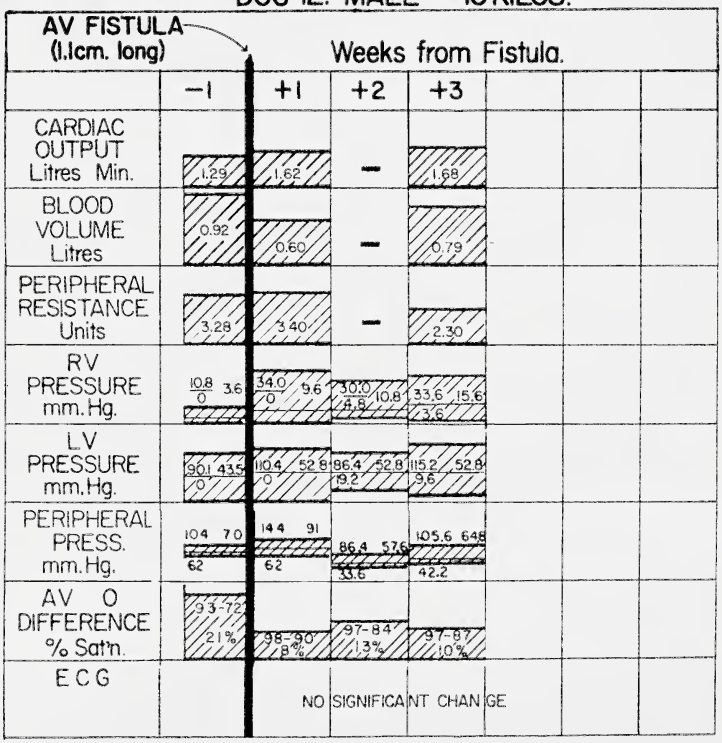
DOG 4 FEMALE 9 KILOS.

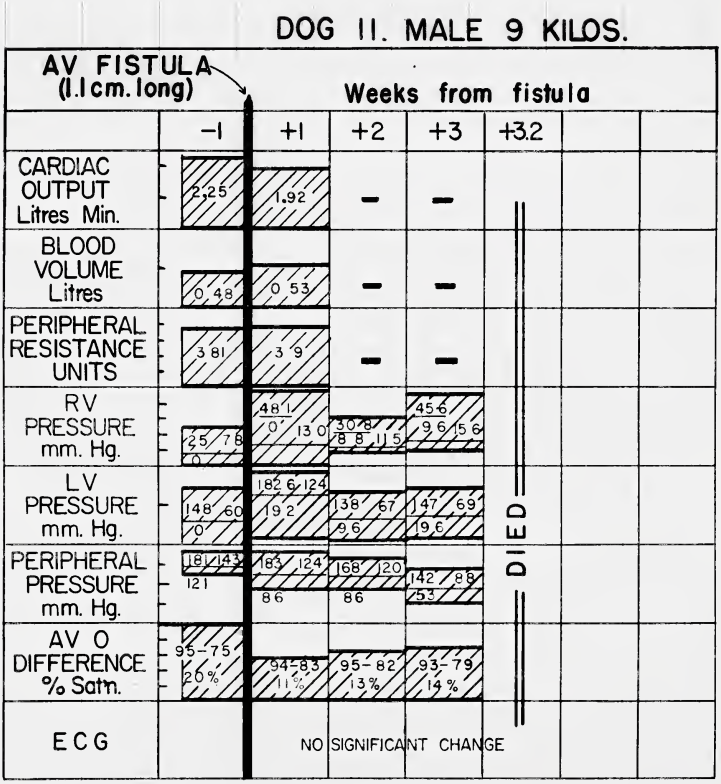


DOG 9 MALE 10 KILOS.

AV FISTULA (1.0 cm. long)	Weeks from fistula						
	−2	+1	+2	+3	+4	+5	+6
CARDIAC OUTPUT Litres Min.	—	2.25	3.1	1.17	3.8	2.64	3.29
BLOOD VOLUME Litres	—	—	0.4	0.55	0.72	0.72	—
PERIPHERAL RESISTANCE UNITS	—	2.55	1.79	2.24	1.55	2.1	1.9
R V PRESSURE mm. Hg.	11.7 / 0 48	37.8 15.3 / 0	40.0 16.2 / 4.0	21.0 / 0 11.2	25.0 / 0 7.2	36.0 9.6 / 0	45.6 / 4.8 16.8
L V PRESSURE mm. Hg.	172 68 / 0	150 95 / 0	110 55.0 / 7.0	99 / 3.2 56	137 56 / 0	120 48 / 5	120 60 / 24
PERIPHERAL PRESSURE mm. Hg.	168 / 132 148	185 / 122 140	110 92.5 / 65	99.2 / 41.6 64	137 98.4 / 78.4	120 / 67 91	134.4 100.8 / 72
AV O_2 DIFFERENCE % Sat'n.	—	—	—	—	81—74 / 7%	90—82 / 8%	61—48 / 13%
E.C.G			NO SIGNIFICANT CHANGE				

DOG 12. MALE 10 KILOS.




DOG 11. MALE 9 KILOS.
AV FISTULA (1.1cm. long)
Weeks from fistula
-1
+1
+2
+3
+3.2
CARDIAC OUTPUT Litres Min.
2.25
1.92
BLOOD VOLUME Litres
0 48
0 53
PERIPHERAL RESISTANCE UNITS
3 81
3 9
RV PRESSURE mm. Hg.
25/ 7 8
0
48 1
0 13 0
30 8
8 8 11 5
45 6
9 6 15 6
LV PRESSURE mm. Hg.
148 60
0
182 6 124
19 2
138 67
9 6
147 69
19 6
PERIPHERAL PRESSURE mm. Hg.
181 143
121
183 124
86
168 120
86
142 88
53
AV O DIFFERENCE % Satn.
95-75
20%
94-83
11%
95-82
13%
93-79
14%
DIED
ECG
NO SIGNIFICANT CHANGE

DISCUSSION

SERIES A

The unfortunate results obtained from the dogs in Series A need little elaboration. It was largely on this group of animals that the basic techniques and procedures for our determinations were worked out.

It might be noted that work commenced on this project in July of 1954 and that in December of 1954 our first complete base-line determinations were obtained. In January of 1955 we first noted hemodynamic values following the establishment of an arterio-venous fistula. By March of 1955 the technique as being used at present was fully evolved.

We were able to find but one reference in the literature to a determination of cardiac outputs by measurement of the concentration of Evan's blue dye in whole blood.[44] Shadle et al evaluated their results using a cuvette densitometer by comparing them with simultaneous Fick outputs (41 comparisons) and concluded that this method was accurate. (They had their galvanometer response made logarithmic so did not have to replot).

We were unable to find any reference in the literature to a method of calculating blood volumes by recording galvanometer deflections following the injection of dye. Nevertheless, our method of measuring the concentration of T1824 dye in whole blood appeared to be theoretically sound and the results obtained were compatable with expected values. We made no comparison with accepted methods of determining blood volumes.

Since both cardiac output and blood volume determinations were serial ones in which we were more interested in comparative than in absolute values any systematic errors in our techniques should have cancelled out.

The pressure determinations were, in every tracing, measured

during the phase of expiration. This phase, in the anaesthetized dog, was usually 20 to 30 seconds long. We considered that during this time, intrapleural pressure should be very close to zero. The fact that all our animals had measured diastolic pressures of zero in the ventricular cavities before exhibiting clinical signs of failure would appear to substantiate this contention.

SERIES B

Of the eight dogs who died shortly after the establishment of an arteriovenous fistula we were able to obtain physiologic studies following the procedure in one animal. (Dog #10).

At this time the cardiac output and blood volume were decreased from pre-fistula levels with no appreciable change in the peripheral resistance.

This would indicate either that the changes described as occurring following the opening of a shunt (increase in cardiac output and blood volume with a decrease in peripheral resistance) did not do so for some reason in this animal or that the maximum height of these indices had been reached and, at the time of measurement, the heart had commenced to decompensate with a resultant fall in cardiac output and increase in peripheral resistance. The reduced blood volume and the fact that the diastolic pressures in the ventricular cavities showed no elevation would seem to preclude the latter explanation. The dog did exhibit the increased pulse pressure one would expect.

It seems possible that the lack of rise of our variables in this dog might be related to the animal's generalized debility, which was considerable at the time of the measurements. The fact that death ensued a few days later following a minimal dose of nembutal supports this postulate.

Two animals (dogs #2 and #8 B) died rapidly in what was clinically and pathologically acute left ventricular failure following the construction of fistulas of more than what appeared to be our optimum length of 1.0 cm.

SERIES C

Five animals were observed for varying periods of time following the establishment of arterio-venous fistulas.

Dog #4 had a closure of the shunt twelve weeks after its production which was evidenced by a disappearance of the murmur, and by a change in physiologic measurements.

Hemodynamic studies indicated that the fistula was becoming smaller in dog #7. The murmur in this dog was also becoming less distinct.

Three animals showed evidence for heart failure with an elevation of end-diastolic pressure in one or both of the ventricular cavities. One of these, (dog #11) died after several sets of observations had been made.

In no animal was clinical or pathological evidence for sub-acute bacterial endocarditis found. Incidently, Lillehei's observation regarding the increased size of the adrenal glands in dogs with an arterio-venous fistula was not confirmed by us.(27)

Cardiac outputs seemed, generally, to follow the trend which was expected from a review of the literature. Following the establishment of a fistula they increased to a maximum, becoming then smaller only if there was clinical evidence for closure of the shunt or evidence for cardiac failure. We did not obtain the large increases in cardiac output to 5 or 6 times the basal level that several workers have reported.(9,26) It is unfortunate that in two of the animals (dog #12 and dog #11) we were unable to record cardiac outputs at a very critical period soon after they had gone into cardiac failure. (This was because of a lack of recording film

which has a short expiration period, is not stocked in Canada, and must be sent directly from Germany. Some frantic experimentation revealed that Kodak linograph paper was a usable, albeit inferior, substitute).

Our results would appear to substantiate a previously mentioned observation that the cardiac output is not necessarily elevated in the presence of a functioning fistula.(44,10)

A marked discrepency, on the basis of previous discussion, appeared to exist in the values obtained on dog #9 in our last measurements. This animal looked to be, at this time, in clinical cardiac failure and the ventricular pressure measurements would seem to have confirmed the impression. The cardiac output was, however, contrary to expectation, elevated from previous levels. It should be noted that the dog at the time of these determinations, had a fairly pronounced degree of hypoxia with an arterial oxygen saturation of 61%. Richard Gorlin has reported on the circulatory adjustments to hypoxia in normal dogs and states that "when the saturation is less than 60% but greater than 40% cardiac work and output increase, and despite prolonged exposure to hypoxia, cardiac function remains normal up to 8 hours."(15) We might postulate that hypoxia could have some such effect here.

A decrease in cardiac output accompanying functional closure of the fistula is illustrated by dogs #4 and #7.

Our observations on blood volume were difficult to evaluate both because we did not have consistent determinations and also because another variable was introduced by post-operative morbidity following construction of the arterio-venous fistulas. In general, however, the results agreed with those suggesting an increase in blood volume. We were unable to demonstrate the increase prior to the onset of other evidences of decompensation that has been reported elsewhere.(45,47,56)

The peripheral resistance appeared to be consistently related in a negative manner to the degree of shunt obtained. We did not have a sufficient number of determinations following the onset of clinical failure to establish any increase in resistance as a compensatory mechanism.

The changes obtained in the peripheral blood pressure were precisely those reported by all other writers, with an increase in pulse pressure on establishment of the fistula, and a narrowing when the fistula closed. The systemic blood pressure appeared to drop with the onset of failure of the heart.

All the evidence that we were able to accumulate pointed to a primary failure of the left ventricle. The dogs that died rapidly appeared to die in left ventricular failure. Dogs #9, #12 and #11 showed an elevation of end-diastolic ventricular pressure first in the left ventricle. This elevation was followed within a fairly short period of time by an elevation of diastolic pressure on the right side. Evidence indicated that this process is not irreversible for in dog #9 elevated diastolic values were seen in the ventricular cavities two weeks and three weeks after the establishment of the fistula, which subsequently dropped again to zero. (At the time of these measurements the dog exhibited pulmonary rales and moderate quantities of frothy fluid drained from its lungs). Also, a diastolic pressure rise in the right ventricle was accompanied, in one instance, by a moderate drop in the previously elevated left ventricular pressure.

There were an insufficient number of determinations obtained from the pulmonary artery to make any observations regarding pressures here.

Despite the fact that, as previously pointed out, there is no theoretical reason for a correlation between end-diastolic pressures in the ventricle and mean pressure in the adjacent auricle we demonstrated a fairly

good correlation in our admittedly small number of comparisons.

As would be expected from Fick's principle of cardiac output determination, the arterio-venous oxygen difference was decreased immediately following the establishment of our shunts. With the onset of failure, once again as expected from hemodynamic principles, the arterio-venous oxygen differences increased.

We were unable to demonstrate changes in the cardiac silhouette of any dogs in whom arterio-venous fistulas were established.

Similarly serial observations of the electrocardiogram demonstrated no evidence for hypertrophy of either side of the heart.

CONCLUSIONS

Our series was too small and this discussion is too premature for any valid conclusions to be drawn. It would appear, however, that in the "high output" type of failure produced by the effects of an arterio-venous fistula the left ventricle is the first chamber to decompensate, followed by failure of the right ventricle. That the right ventricle should fail in consequence of primary failure of the left ventricle is a reasonable and well accepted chain of circumstances which it is unnecessary to discuss further. The problem is: Why does the left ventricle decompensate first?

The basic physiological change which initiates hemodynamic adjustments leading eventually to decompensation would appear to be the increased cardiac output. This increase is apparently brought about both by an increased fluid volume and by an increased pulse rate. (In our investigation we have been unable to establish any particular increase in pulse rate following the opening of an arterio-venous fistula). These two factors would seem, necessarily, to effect each chamber of the heart to an equal degree. Any increase in fluid volume, increasing the filling pressure on the right side of the heart must very rapidly be transmitted as increased filling pressure to the left side since the output of the two sides must remain equal.

Perhaps because of its smaller capacity, the pulmonary circulation is less able to act as a buffer to an increase in fluid volume than is the systemic circulation. Therefore the left ventricular cavity may take more of the brunt of increased distension than the right ventricular cavity, from which an increased pressure is more widely distributed throughout the entire central venous system.

One might also speculate as to whether there is any intrinsic difference in intracellular metabolism, distensibility characteristics or manner of reacting to stress of the muscle composing the right and left ventricular walls. Such a difference could perhaps lead to primary failure of one side.

We feel it is important that the observations which have been made thus far should be confirmed and extended. X-ray and electrocardiographic changes which have not as yet occurred in our animals, could be expected to take place in a longer period of time.

The possibilities for extension of this investigation are almost unlimited.

A digitalis-like preparation, in the form of Quabain, was administered to dog #11 while physiological measurements were being made. No acute changes of intracardiac pressures were seen. In view of the fact that digitalis appears clinically to have little effect in "high output" failure of the heart further investigation might perhaps be warranted.

The effects of a sodium-free diet should be evaluated.

The evolvement of changes in the liver in congestive heart failure, which has apparently been incompletely understood, could perhaps be studied by serial liver biopsies.

If, later, hypertrophy is definitely demonstrated by our animals with cardiac failure some investigation might be done on the effects of hypophysectomy or of pituitary growth hormone on the process. This is in view of Bernek's observations concerning the dependence of hypertrophy on this hormone.(2)

Because the pulse rate may be an important determining factor in increasing cardiac output a method might be devised for either slowing or controlling the pulse rate of experimental animals and evaluating the

effect of a slow rate on the development of cardiac failure.

An attempt might be made to produce "high output" failure by other means, such as administering thyroid hormone, and to compare the hemodynamic changes with those of arterio-venous fistula.

SUMMARY

1. An attempt has been made to correlate hemodynamic changes with the development of cardiac failure in dogs subjected to an arterio-venous fistula.

2. Hemodynamic measurements made were recordings of pressures in the right ventricle, left ventricle and carotid artery. Determinations of cardiac output, blood volume and peripheral resistance were also obtained.

3. To make these determinations possible the animals were first subjected to a carotid transplant and cardiopexy. Some time later an anastomoses was effected between the aorta and the inferior vena cava.

4. Of a total of 26 animals operated upon, 13 reached the stage of having an arterio-venous fistula constructed. Five of these were followed for an appreciable period of time after the procedure.

5. Three dogs showed evidence of cardiac failure with an initial elevation of end-diastolic pressure in the left ventricle followed, fairly rapidly, by an elevation of end-diastolic pressure in the right ventricle.

6. The remaining two dogs gave both clinical and hemodynamic evidence for a closure of the arterio-venous fistula.

PART IV

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Allison, J. T. and Linden, L. Bronchoscopic Approach for Measuring in Left Auricle, Pulmonary Artery and Aorta. Lancet 9-13 (Jan.) 1955.

2. Beznak, M. The Effects of the Adrenals and Pituitary on Blood Pressure and Cardiac Hypertrophy of Rats. J. Physiol., 116;219-223. 1952.

3. Bjork, V. O., Malmstrom, G., and Uggla, L. G. Left Ventricular Pressure Measurements in Man. Ann. Surg. 138; 718-722 (Nov.) 1953.

4. Blake, W. D., Wegria, R., Keating, R. P. and Ward, H. P. Effect of Increased Renal Venous Pressure on Renal Function. Am. J. Physiol. 175; 1-12. 1947.

5. Cohan, S. M., Edholm, O. G., Howarth, McMichael, J. and Sharpey-Schafer, E. P. Cardiac Output and Peripheral Blood Flow in Arterio-Venous Aneurism. Clinical Science 7; 35-41. 1948.

6. Doyle, J. T., Wilson, J. S., Lepine, C., and Warren, J. V. An Evaluation of the Measurement of Cardiac Output and the so-called Blood volume by the Dye Dilution Method (J. Laborat. Clin. M.) 41:29-39, 1953.

7. Edholm, O. G., Howarth, S. and McMichael, J. Heart Failure and Bone Blood Flow in Osteitis Deformans. Clin. Sc. 5; 249-260. 1945.

8. Epstein, F. W., Post, R. S. and McDowell, M. The Effect of an Arterio-Venous Fistula on Renal Hemodynamics and Electrolyte Excretion. J. Clin. Invest. 32; 233-239. 1953.

9. Epstein, F. W., Shadle, O. W., Ferguson, T. B. and McDowell, M. E. Cardiac Output and Intracardiac Pressures in Patients with Arterio-Venous Fistulas. J. Clin. Invest. 32; 543-547 (June) 1953.

10. Ellis, L. B. and Weiss, S. The Local and Systemic Effects of an Arterio-Venous Fistula on the Circulation in Man. Am. Heart J. 5; 635-642. 1930.

11. Ferguson, T. B., Shadle, O. W., and Gregg, D. E. Effects of Blood and Saline Infusion on Ventricular and Diastolic Pressure, Stroke Work, Stroke Volume and Cardiac Output in the Open and Closed Chest Dog. Circul. Res. Vol. 1; 62-68 (Jan.) 1953.

12. Freidburg, C. K. Diseases of the Heart. W. B. Saunders & Co., 1950.

13. Gibson, J. G. and Evans, W. A.,Jr. Clinical Studies of Blood Volume III, Changes in Blood Volume, Venous Pressure and Blood Velocity Rates in Chronic Congestive Heart Failure. J. Clin. Invest. 16; 851-862. 1937.

14. Gibbon, J. H. and Churchill, E. D. Changes in the Pulmonary Circulation Induced by Experimentally Produced Arterio-Venous Fistula. Arch. Surg. 21; 1188-1194. 1930.

15. Gorlin, R. and Lewis, B. Circulatory Adjustments to Hypoxia in Dogs. Appl. Physiol. 180-185 (Sept.) 1954.

16. Hamilton, W. F., Kinsman, J. M. and Moore, J. W. Studies on the Circulation -- I Injection Method - Physical and Mathematical Considerations. J. Clin. Invest. 89; 322-330. 1929.

17. Hamilton, W. F. Blood Volume. Medical Physics -- Volume One. Otto-Glasser. Year Book Publishers. 1950.

18. Hamilton, W. F., Moore, J. W., Kinsman, J. M. and Sparling, R. D. Studies on the Circulation; IV. Further analysis of the Injection Method, and of the Changes in Hemodynamics under Physiological and Pathological Conditions. Am. J. Physiol., 99; 534-551 (Feb.) 1932.

19. Hamilton, W. F. The Physiology of Congestive Failure of the Circulation. Minnesota M. 37; 77-130 (Feb.) 1954.

20. Hampden, C. L., Shadle, O. W., Coleman, E. S., and Holtgrave, D. E. A Comparison of Intracardiac and Intravenous Injections for the Measurement of Cardiac Output - by the Dilution Teachnique. Circul. Res. II 251-253 (May) 1954.

21. Holman, E. Arteriovenous Aneurysm, Abnormal Communication Between the Arterial and the Venous Circulations. MacMillan, New York. 1937.

22. Isaacson, J. and Jones, R. E. An Electromagnetic Hydraulic Transducer for Studying Response Characteristics of Manometer Systems to Square Wave and Sine Wave Pressure Variations of Variable Frequency. Am. J. Physiol. 163; 722-723. 1950.

23. Katz,L.M. The Mechanism of Cardiac Failure. Circulation 10:5 663-679 (Nov.) 1954.

24. Lawson, H. D., Bloomfield, R. A. and Cournand, A. The Influence of Respiration on the Circulation in Man. Am. J. Med. 1; 315-323. 1946.

25. Lewis, T. and Drury, A. N. Observations Relating to Arterio-Venous Aneurism. Heart 10; 301-314. 1923.

26. Lillehei, C. W., Bobb, J. R. R. and Visscher, M. B. Effect of Arterio-Venous Fistulas Upon Pulmonary Arterial Pressure, Cardiac Index, Blood Volume and the Extracellular Fluid Space. Surg. For. 275-282, 1950.

27. Lillehei, C. W., Bobb, J. R. R. and Visscher, M. B. The Occurrence of Endocarditis with Valvular Deformities in Dogs with Arterio-Venous Fistulas. Ann. Surg. 132; 577-589 (Oct.) 1950.

28. Markowitz, J. Experimental Surgery - III Edition, p. 632. Williams and Wilkins.

29. Merrill, A. J. Edema and Decreased Renal Blood Flow in Patients with Chronic Congestive Heart Failure: Evidence of Forward Failure and the Primary Cause of Edema. J. Clin. Invest. 25; 389-396. 1946.

30. Merrill, A. J. Mechanics of Salt and Water Retention in Heart Failure. Am. J. Med. 6; 357-367 (March) 1949.

31. McMichael, J. Cardiac Venous Congestion -- Its Causes and Consequences. Am. J. Med. 6; 651-661 (May) 1949.

32. Nickerson, J. L., Cooper, F. W., Jr., Robertson, R. L. and Warren, J. V., Arterial, Atrial and Venous Pressure Changes in the Presence of an Arterio-Venous Fistula. Am. J. Physiol. 167; 426-434. 1951.

33. Paines, R., and Smith, J. R. The Mechanism of Heart Failure. Am. J. Med. 6; 84-102 (Jan.) 1949.

34. Patterson, S. W., Piper, H. and Starling, E. H. The Regulation of the Heart Beat. J. Physiol. 48; 465-471. 1914.

35. Peters, J. P. Role of Sodium in the Production of Edema. N. England J. M. 333-239. 1948.

36. Raat, W. Hormonal Factors in Heart Disease: Their Role in Myocardial Hypertrophy, Hypoxia, and Electrolyte Imbalance. Ann. Int. Med. 41; 757-763 (Oct.) 1954.

37. Rubens, R. E., Geraci, J. E., Grindley, J. H., and Karlson, A. G. Experimental Bacterial Endocarditis Due to Streptococcus mitis. Circulation 9; 199-214 (Feb.) 1955.

38. Richards, D. W. Dynamics of Congestive Heart Failure. Am. J. Med. 6; 772-779 (June) 1949.

39. Roos, A., and Smith, J. R. The Production of Experimental Heart Failure in Dogs with Intact Circulation. Am. J. Physiol. 153; 558-567. 1948.

40. Rushmer, R. F. Continuous Measurement of Left Ventricular Dimensions in Intact, Unanaesthetized Dogs. Circulation Research II; 14-21 (Jan.) 1954.

41. Sarnoff, S. J., and Berglund, E. Starling's Law of the Heart Studied by means of Simultaneous Right and Left Ventricular Function Curves in the Dog. Circulation 10; 706-719 (May) 1954.

42. Schriener, G. E., Frienkel, N., Athens, J. W. and Stone, W. Cardiac Output, Control Volume and Dye Injection Curves in Traumatic Arterio-Venous Fistulas in Man. Circulation 7; 718-723. May 1953.

43. Schriener, G. E., Frienkel, N., Athens, J. W., and Stone ". Dynamics of T-1824 Distribution in Patients with Traumatic A-V Fistulas. Circul. Res. I; 548-553 (Nov.) 1953.

44. Shadle, O. W., Ferguson, T. B., Gregg, D. E., and Gillford, S. R. Evaluation of a New Cuvette Densitometer for Determination of Cardiac Output. Circul. Res. I: 200-205 (May) 1953.

45. Stead, A. The Role of the Cardiac Output in the Mechanisms of Congestive Heart Failure. Am. J. Med. 6; 232-236 (Feb.) 1949.

46. Stead, E. A., Jr., and Warren, J. V. Cardiac Output in Man. An Analysis of the Mechanisms Varying Cardiac Output Based on Recent Clinical Studies. Arch. Int. Med. 80; 237-248. 1947.

47. Vanloo, A., and Herringnam, E. C. Circulatory Changes in the Dog Produced by Acute Arterio-Venous Fistula. Am. J. Physiol. 158; 103-112. 1949.

48. Warner, H. R., and Wood, E. H. Simplified Calculation of Cardiac Output from Dye Dilution Curves Recorded by Oximeter. J. Appl. Physiol. 5; 111-116 (Sept.) 1952.

49. Warren, J. V., Elkin, D. C., and Nickerson, J. L. The Blood Volume in Patients with Arterio-Venous Fistulas. J. Clin. Invest., 30; 220-226. 1951.

50. Warren, J. V., Nickerson, J. L., and Elkin, D. C. The Cardiac Output In Patients with Arterio-Venous Fistulas. J.Clin. Invest., 30; 210-220, 1951.

51. Warren, J. V., Brannan, E. S. and Cooper, F. W. The Hemodynamics of Rapid Changes in Cardiac Output in Man. J. Clin. Invest. 26; 1199-1208. 1947.

52. Whiting, G. and Hoty, L. F. An Evaluation of the Evan's Blue Dye — T1824 Method for Studying Circulatory Blood Volume. Surg. Gyn. Obst. 97; 709-716 (Dec.) 1953.

53. Wiggers, Carl J., Dynamics of Ventricular Contraction Under Abnormal Conditions. Circulation 5; 3; 321-348 (March) 1952.

54. Wise, W., Meyer, J., Katz, L. N., Lendrum, B. and Jachim, K. The Oxygen Consumption and Mechanical Efficiency of the Heart Before and During Heart Failure. Am. J. Physiol. 147; 28 1946.

55. Wood, E. H. and Nichalson, J. W. III. A Direct Reading Cuvette Oximeter and Strain Gauge Manometer Assembly for Measurement of Blood Oxygen Saturation and Continuous Recording of Arterial Pressure and Continuous Recording of Arterial Pressure and Time -- Concentration Curves of Evan's Blue Dye in Arterial Blood of Man. Am. J. Physiol. 163; 762-763 (Dec.) 1950.

56. Youmans, W. B. Mechanics of High Output Circulatory Failure. Ann. Int. Med., 41; 747-757 (Oct.) 1954.

57. Youmans, W. B. Renal Function in Congestive Heart Failure. Ann. Int. Med. 41; 739-747 (Oct.) 1954.

PART V

APPENDIX

APPENDIX

1. DOG #7, 10 kilograms. Cardiac Output and Pressure Determinations

January 14th, 1955.

2:50 p.m. — control blood sample taken prior to cardiac output determination.

2:52 p.m. — Evan's blue dye 6.75 mgm. injected from calibrated syringe through #4 catheter and stopcock into right ventricle.

Blood collected immediately from arterial needle into tubes rotating on kymograph beneath collecting needle. When tubes spun down there was no evidence of dye in the plasma until tube #7.

RESULTS

TUBE NO.	GALVANOMETER READING	(2-log galvanometer read'g) OPT. DENSITY
1	100	0
7	92°	0.036
8	74°	0.131
9	58°	0.237
10	55'	0.258
11	61°	0.215
12	73°	0.137
13	82°	0.086
14	88^2	0.056
15	91^2	0.039

The optical densities were plotted vs. tube number on semi-logarithmic graph paper (see accompanying graph). As can be seen, at tube #14 recirculation becomes evident. A straight line was therefore joined through the points marking the optical density of tubes Nos. 11, 12 and 13 and this was extended to an optical density of 0.01. This cut the base-line at a point corresponding to 17.6 tubes.

The values obtained by thus extrapolating the descending limb of the dye curve were replotted back to linear graph paper. Since the curve does not start until tube #7 it can be seen that the base line is 17.6 — 6 or 11.6 tubes (= 14.6 cm. on graph).

The curve this formed was cut out, and, along with a 10 cm. square from the same sheet, was weighed. The area bounded by the curve was obtained from the formula — Area in sq. cm. = $\frac{\text{Wt. of curve}}{\text{Wt. of 10 cm.sq.}}$ x 100 sq. cm.

$\frac{0.1228 \text{ gm.}}{0.3163}$ x 100 = 38.8 sq. cm

The mean concentration of dye corresponds to the average height of the dye curve which is equal to the $\frac{\text{area sq. cm.}}{\text{base in cm.}} = \frac{38.8 \text{ sq. cm.}}{14.0 \text{ cm.}} = 2.66$ cm.

On our scale 2.66 = 0.106 optical density.

1.95 cm. = 0.095 optical density.

Now, using a previously constructed calibration curve in which known amounts of dye were added to water and the optical density recorded we find that optical density 0.106 = 25.7 mgm. of Evan's blue dye per litre.

The time taken for the base-line of our curve to be inscribed = 11.6 (tube no.) x 1.3 seconds (speed of the kymograph) = 15.03 seconds.

The formula for cardiac output is:

$$F = \frac{Q \times 60}{C \times t} \times \frac{100}{ht}$$

Where F = flow in litres of blood per minute.

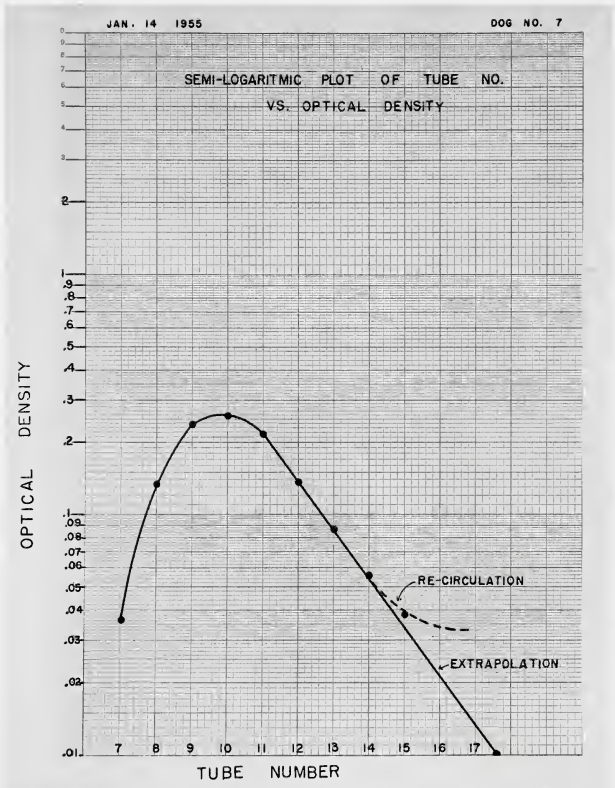
Q = quantity of dye injected in mgm.

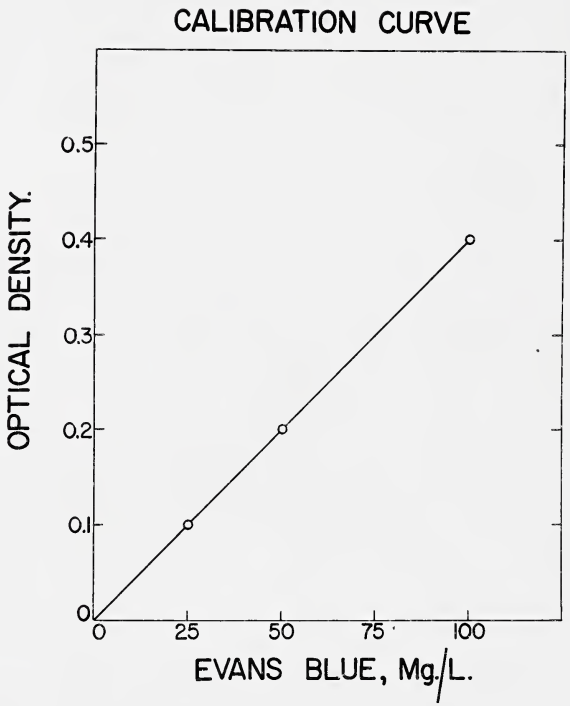
C = mean concentration of dye in mgm./litre.

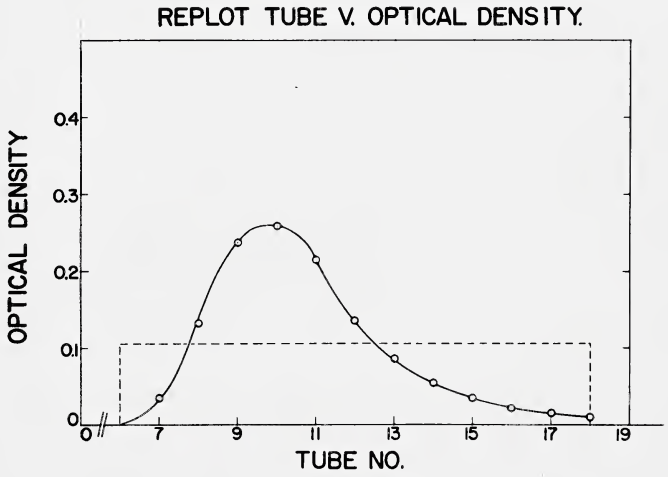
t = time in seconds.

Ht = hematocrit.

Substituting in this formula — C.O. = $\frac{6.75 \times 60 \times 100}{25.7 \times 15.0 \times 53} = 1.98$ L./min.


JAN. 14 1955
DOG NO. 7
SEMI-LOGARITMIC PLOT OF TUBE NO.
VS. OPTICAL DENSITY
OPTICAL DENSITY
TUBE NUMBER
RE-CIRCULATION
EXTRAPOLATION
7
8
9
10
11
12
13
14
15
16
17


CALIBRATION CURVE
OPTICAL DENSITY.
0.5
0.4
0.3
0.2
0.1
0
0
25
50
75
100
EVANS BLUE, Mg./L.


REPLOT TUBE V. OPTICAL DENSITY.
OPTICAL DENSITY
0.4
0.3
0.2
0.1
0
0
7
9
11
13
15
17
19
TUBE NO.

Blood Volume

	Hematocrit	Galv. R.	O.D.
Sample # 1 = (prior to dye injection)	53	100	0.
Sample # 2 = (taken at 3:02 p.m. 10 min. after injection)	54	4^2	.1349
Sample # 3 = (taken at 3:12 p.m. 20 min. after injection)	53	4^2	.1349

Extrapolating back to 0 time -- the optical density at 0 time = 0.1349. Again, using our calibration curve --

0.1349 = 35.5 mgm. dye/litre. Therefore, plasma volume = $\frac{\text{amt. dye injected}}{\text{conc. of dye in plasma}}$

Amt. of dye injected = amt. of dye injected for cardiac output $\pm$ amt. left in catheter and stopcock.

6.75 mgm. $\pm$ (0.5 c.c. x 5 mgm.) =

6.75 mgm. $\pm$ 2.5 mgm. =

9.25 mgm. dye.

Therefore, plasma volume = $\frac{9.25}{35.5}$ = 0.26 litres.

blood volume = 0.26 x $\frac{100}{53}$ = 0.49 litres.

Peripheral Resistance = $\frac{\text{carotid artery pressure x 60}}{\text{C.O. in c.c./min.}} = \frac{190 \times 60}{1980}$ = 5.8 units.

Pulse rate = 200/min.

2. DOG # 11 - 8.5 kilograms. Cardiac Output and Pressure Determinations

June 2nd, 1955.

8:05 a.m. -- unable to perform venapuncture. Given nembutal 35 mgm./kg. intraperitoneally.

9:20 a.m. -- asleep -- electrocardiogram taken.

Unable to puncture right external jugular vein. Cut-down done over left external jugular -- lateral to carotid tube. Catheter stuck above clavicle when introduced at this site. Cut-down done above clavicle. Thrombus removed from vein with small forceps, -- catheter successfully introduced. No. 18 needle introduced into carotid artery (no difficulty).

10:30 a.m. — blood withdrawn through Wood's cuvette for arterial oxygen saturation. Saturation = 94%. Oxygen saturation in right ventricle = 83%. A-V oxygen difference = 11%.

10:45 a.m. — 7.93 mgm. of Evan's blue dye introduced through a #5, 3-hole cardiac catheter into the right ventricle. Blood simultaneously withdrawn through the cuvette and the resultant dye curve recorded on the camera. Time clock set for 10 minutes (blood volume).

10:50 a.m. — Blood with concentrations of 0, 10 mgm./litre, 20 mgm./litre, and 40 mgm./litre of Evan's blue dye drawn through cuvette.

10:55 a.m. — blood for first blood volume deflection drawn through cuvette.

11:05 a.m. — blood for second blood volume deflection drawn through cuvette.

11:15 a.m. — blood for third blood volume deflection drawn through cuvette.

Camera unloaded in dark room and film developed using standard x-ray solutions and procedure.

Pressures from right ventricle, right auricle, left ventricle and carotid artery recorded in the course of the previous procedure.

CALCULATIONS

Cardiac Output — see accompanying graphs.

Base line of curve = 13.6 cm.

$$\text{Area of curve} = \frac{\text{Wt. of graph}}{\text{Wt. of 10 cm. sq.}} \times 100 = \frac{0.1082}{0.2892} \times 100 = 37.4 \text{ cm.}$$

$$\text{Mean concentration} = \frac{\text{Area of curve}}{\text{Base}} = \frac{37.4 \text{ cm.}^2}{13.6 \text{ cm.}} = 2.75 \text{ cm.}$$

Calibration (from graph)

0 — 10 gamma = 2.50 cm.

10 — 20 gamma = 1.65 cm.

20 — 40 gamma = 3.20 cm.

40 gamma = 7.35 cm.

1 cm. = 5.44 gamma

Rate

4.1 cm. = 5 sec. (time lines are 2.5 seconds apart).

1 cm. = 1.22 seconds.

Time of curve = base in cm. x rate = 13.6 x 1.22 = 16.6 sec.

Mean Concentration (dye) = 2.75 x 5.44 = 14.96 gamma/c.c. or 14.96 mgm./litre.

Cardiac Output = $\frac{\text{Amt. of dye injected}}{\text{Mean concentration}} \times \frac{60}{\text{time in seconds}} =$

$$\frac{7.93}{14.96} \times \frac{60}{16.6} = \frac{476.1}{248.3} = 1.92 \text{ litres/minute}$$

Peripheral Resistance = $\frac{\text{mean carotid artery pressure} \times 60}{\text{cardiac output in c.c.'s}} =$

$$\frac{124.8 \times 60}{1920} \times 3.9 \text{ units.}$$

Blood Volume = Galvanometer deflection in 30 minutes = 2.6 cm.

Galvanometer deflection in 20 minutes = 2.9 cm.

Galvanometer deflection in 10 minutes = 3.4 cm.

(Extrapolating) galvanometer deflection in 0 min. = 3.8 cm.

3.8 cm. = 3.8 x 5.44 = 20.5 gamma of dye/c.c.

20.5mgm. of dye/litre.

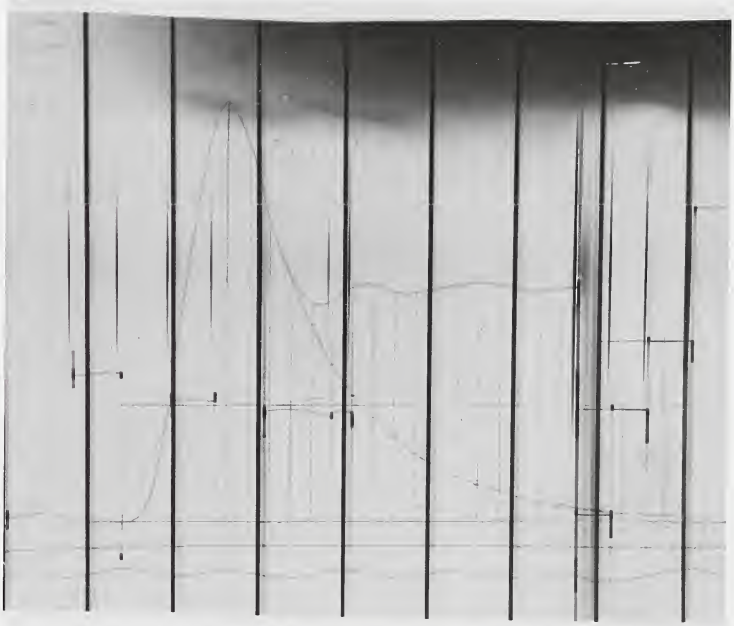
Blood volume = $\frac{\text{amount of dye injected in mgm.}}{\text{conc. of dye in mgm./litre.}}$

Total amount of dye injected = amount delivered through catheter at time of cardiac output and residual amount in the catheter and stopcock.

= 7.93 + 3.0 mgm.

= 10.93 mgm. of dye.

Blood volume = $\frac{10.93 \text{ mgm.}}{20.5 \text{ mgm/litre.}}$ = 0.53 litres.



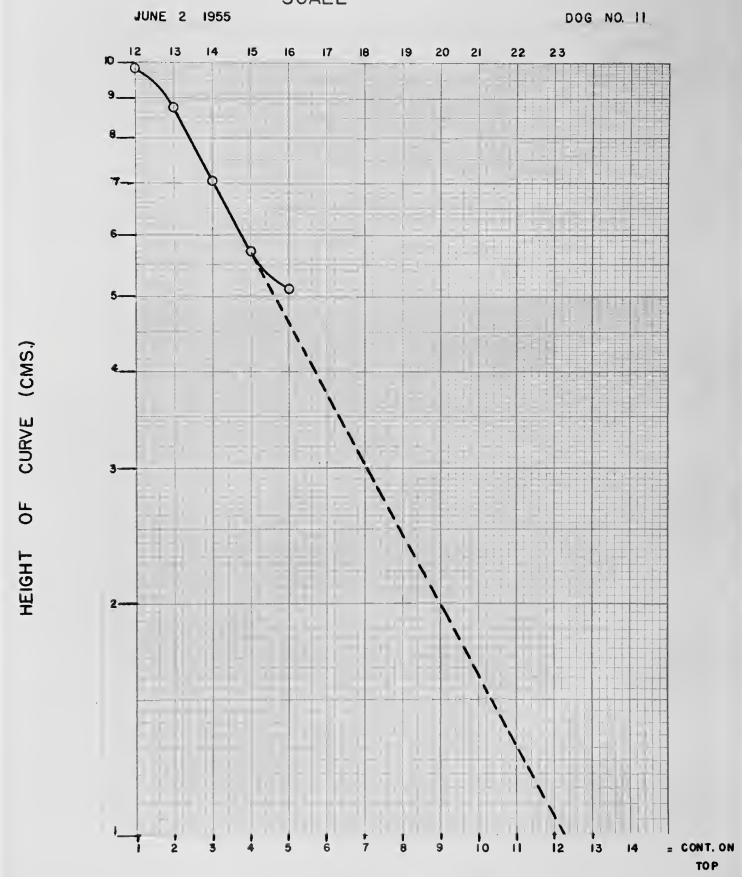
OUTPUT CURVE BY CAMERA METHOD

JUNE 2 1955 DOG II.

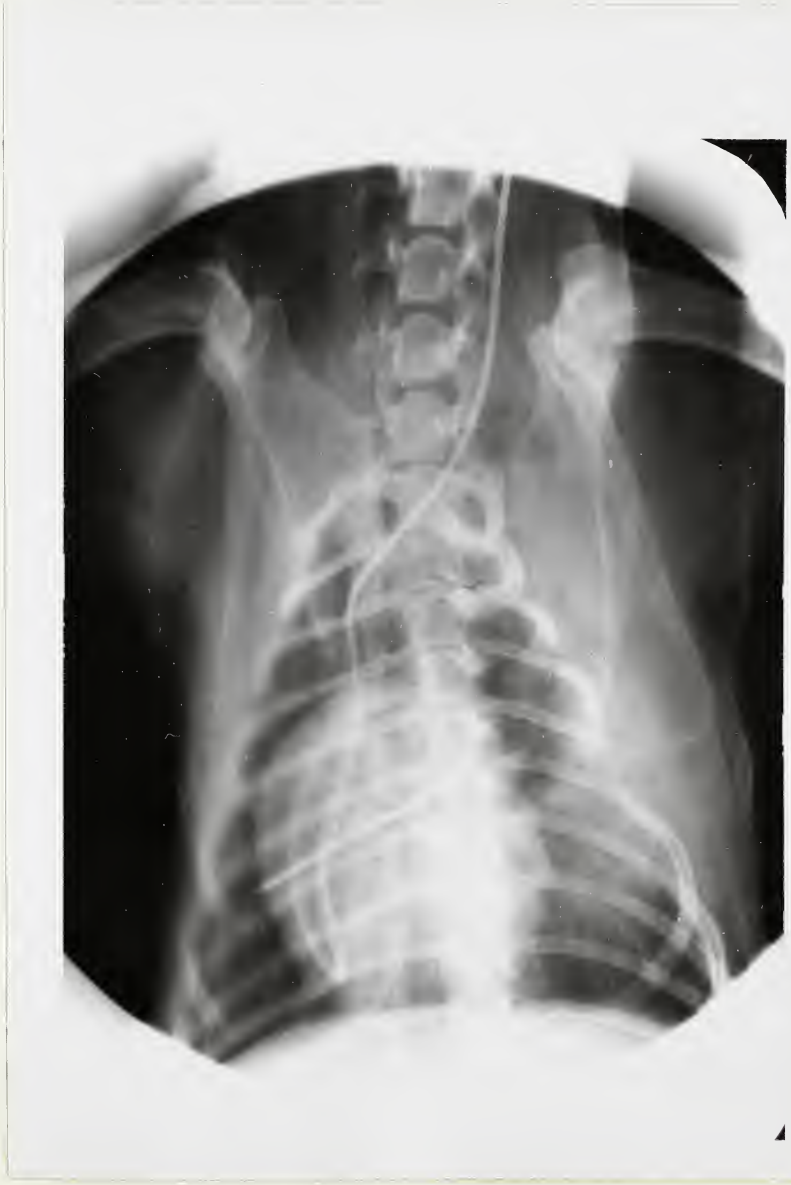
EXTRAPOLATION OF DYE CURVE

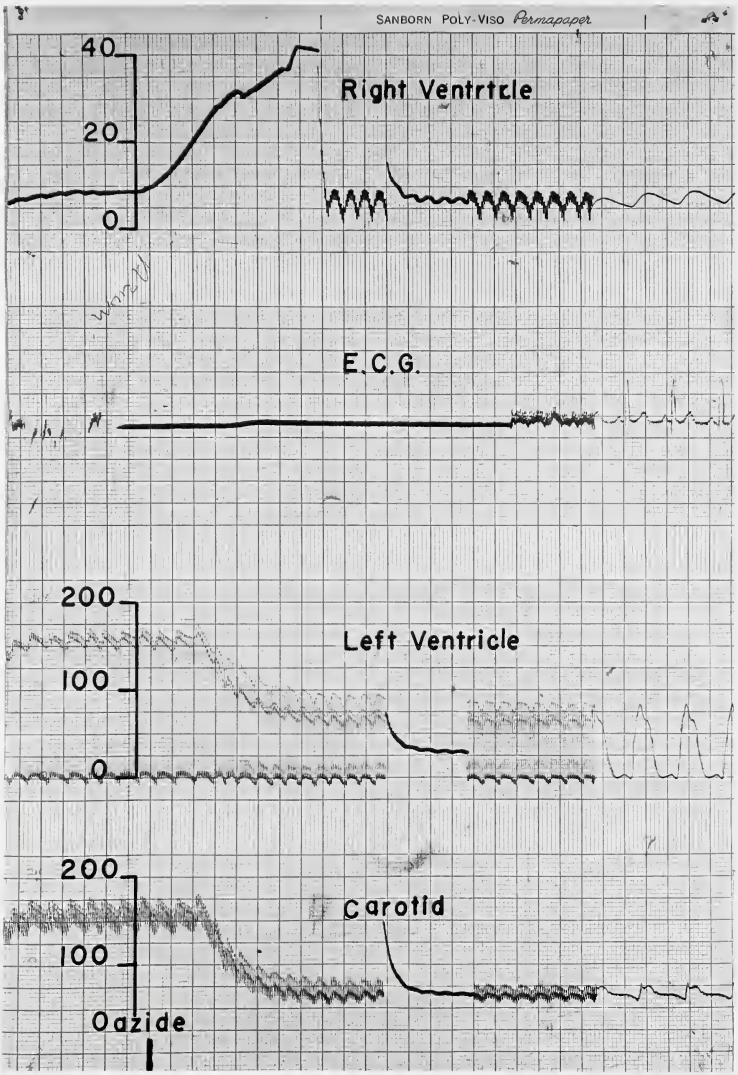
ON SEMI-LOGARITHMIC

SCALE



X-RAY OF DOG WITH CATHETER IN SITU




SANBORN POLY-VISO Permapaper
40
20
0
Right Ventricle
E.C.G.
200
100
0
Left Ventricle
200
100
Carotid
Azide